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JUNE 1959

DISEASES of the CHEST

OFFICIAL PUBLICATION

Silver Anniversary Year

Homecoming Meeting
Albuquerque, New Mexico, October 14-17, 1959

Interim Session
Dallas, Texas, November 29-30, 1959

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OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

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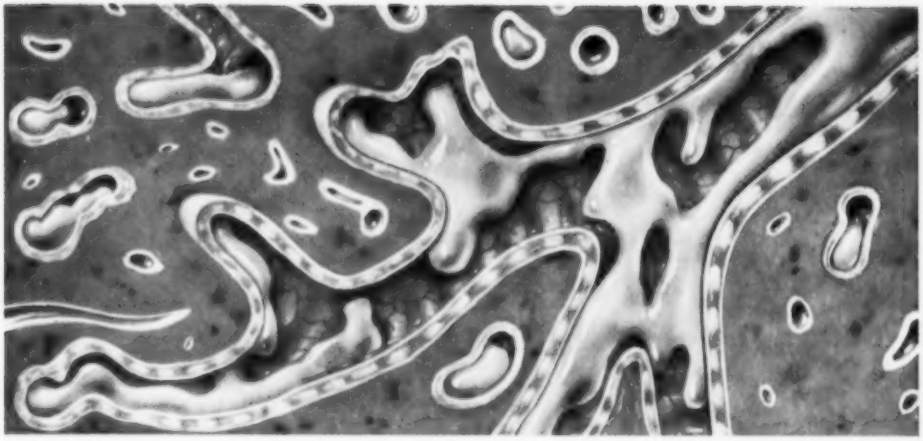

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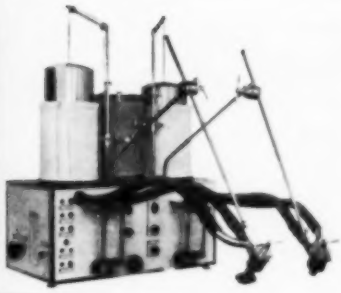

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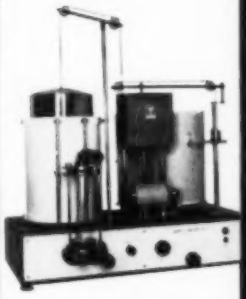

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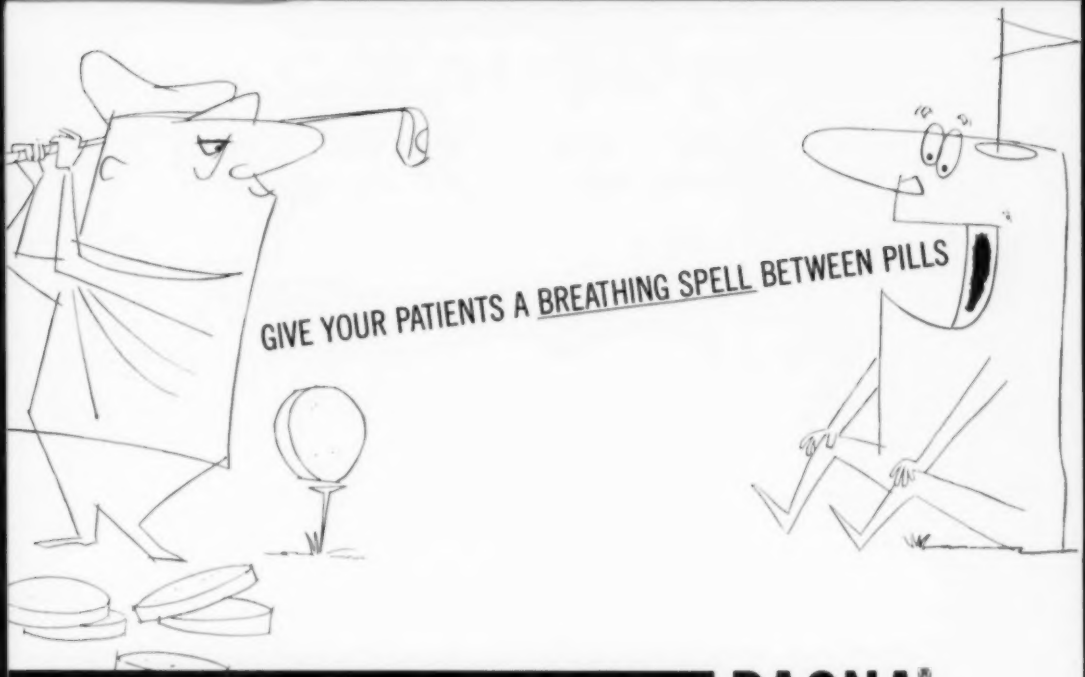

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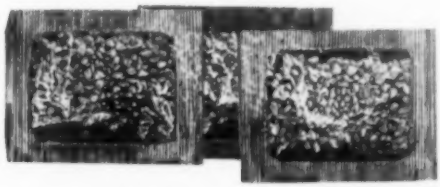

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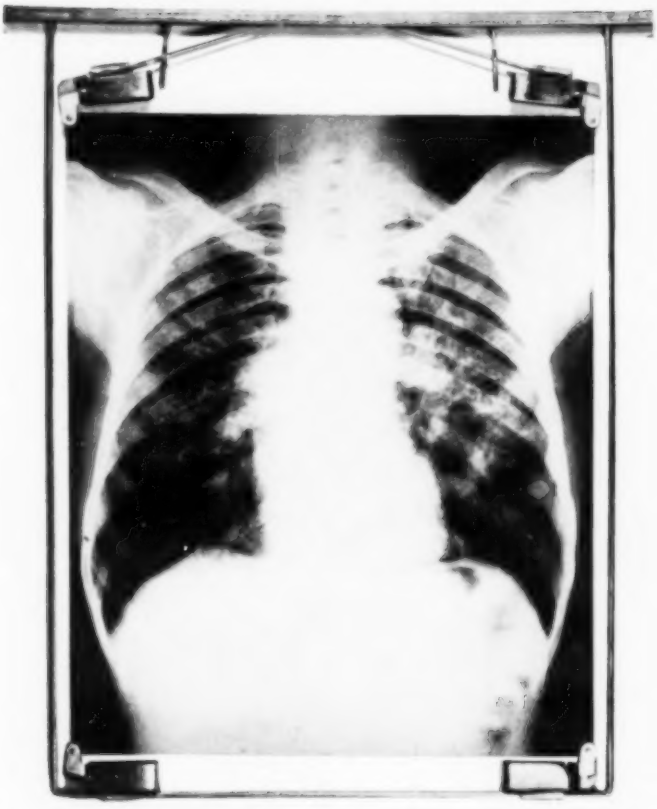

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References: 1. McLean, R. L., and Benson, W. P.: Tr. 15th Conference on Chemotherapy of Tuberculosis, 1956, p. 122. 2. Murdoch, J. M., and Stewart, S. M.: Brit. J. Tuberc. 50:85 (Jan.) 1956.

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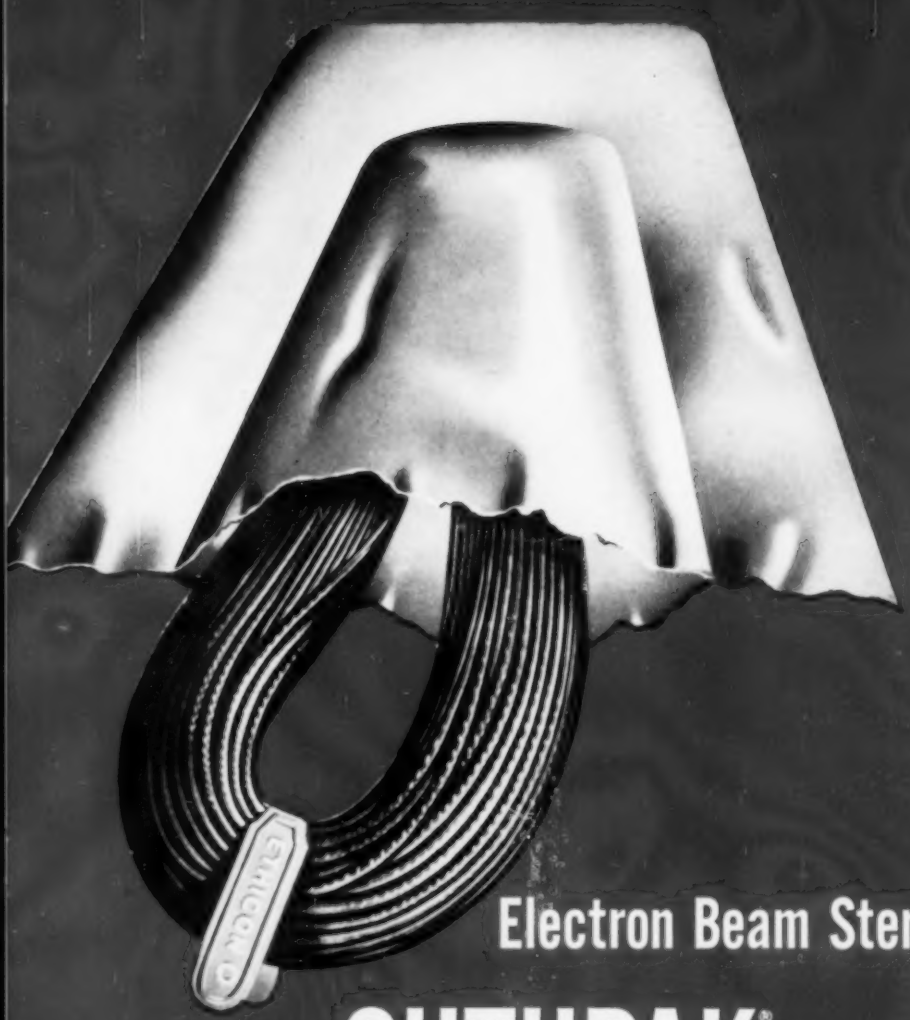

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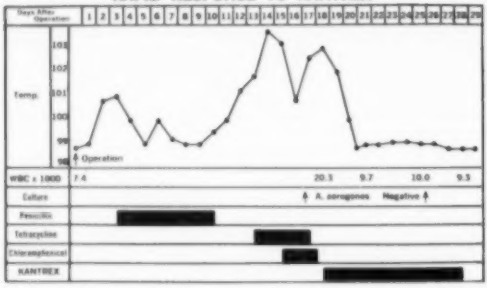

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REFERENCES: • 1. Freyberg, R. H., Berntsen, C. A., Jr., and Hellman, L.: Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.

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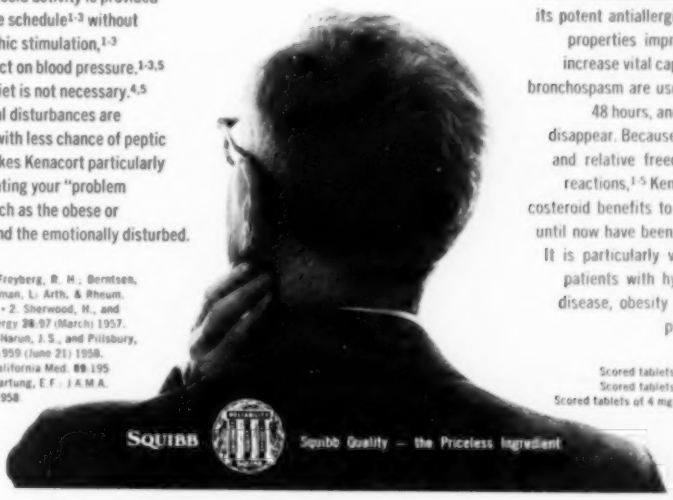

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30	20,000	27,000
31	20,000	24,000
32	20,000	22,000
33	20,000	
34	19,064	
35	18,068	
36	17,042	
37	16,096	
38	15,174	
39	14,260	
40	13,410	
41	12,586	
42	11,794	
43	11,040	
44	10,320	
45	9,634	
46	8,990	
47	8,372	
48	7,798	
49	7,246	
50	6,736	
51	6,254	
52	5,802	
53	5,378	
54	4,982	
55	4,614	
56	4,272	
57	3,952	
58	3,656	
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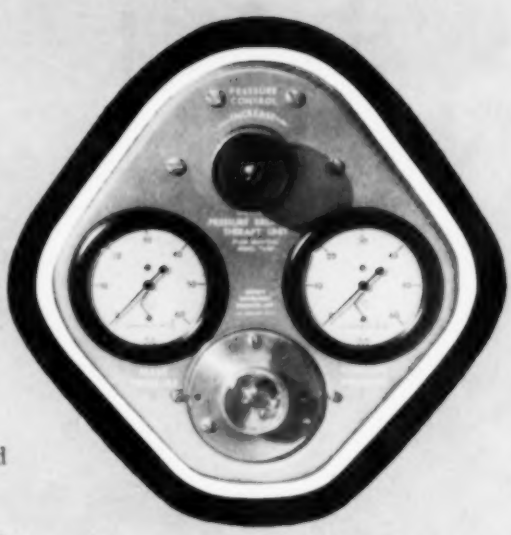

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DISEASES of the CHEST

VOLUME XXXV JUNE, 1959 NUMBER 6

Trigger Mechanisms in Asthma

RICHARD H. OVERHOLT, M.D., F.C.C.P.*

Boston, Massachusetts

The ingenuity of the chest specialist may be taxed to the limit in the management of intractable asthma. Attacks can be frightening and cruel. Responses to therapy are often unpredictable. Underlying factors influencing the intense and generalized bronchospasm are complex. They include: allergy, emotional disturbances, disharmony of sympathetic and parasympathetic nerve control, infection, mucosal thickening and problems of secretion elimination. Although asthma is considered to be a medical disease, irreversible structural changes in the bronchial system may exist. The presence of such mechanical problems should be determined and consideration given to their correction. It is the purpose of this paper to relate some experiences in the search for and the treatment of structural abnormalities which act as "trigger mechanisms."

Historical

The interest of thoracic surgeons in the serious plight of the asthmatic was first kindled by the physiologic work on the nerve control of the lung. More than 100 years ago, Williams[1] investigated the influence of the vagus nerve on bronchial caliber. However, it was the monumental works of Dixon and Brodie[2] and Dixon and Ransom[3] which established the facts that: (1) the preponderance of constrictor fibers are found in the vagus; (2) the preponderance of dilator fibers are in the sympathetic (T1-T2-T3); (3) both systems carry both types of fibers; and (4) fibers cross from right to left and vice versa. Kummel[4] in 1923 was the first to treat asthma by the removal of the stellate ganglia. Since then, there have been many attempts to relieve bronchospasm by interrupting the nerve supply to the lung.** In 1950, at the meeting of the American Association for Thoracic Surgery, three presentations on denervation for asthma were given. Klassen[5] reported on results of vagal section. Abbott[6] combined upper thoracic sympathectomy and plexectomy. Blades[7] emphasized the importance of a complete plexectomy.

In the past, the attention of most surgeons centered on interventions which interrupted the efferent or afferent nerve pathways to the lung. Structural abnormalities were not hunted for and corrected, if present.

*Thoracic Surgeon, New England Deaconess Hospital and New England Baptist Hospital, Boston. Director, Overholt Thoracic Clinic.

**In a recent paper, the author included a more detailed historical account of surgical procedures which have been carried out in asthmatic subjects.[8]

Overlooked "triggers" quite possibly contributed to disappointing lasting results of denervation alone. However, it has been recognized that disturbances in one area of the bronchial system may act as a "trigger" to set off general bronchospasm. Abbott[6] advised that destroyed segments be removed at the time the lung was being denervated. In 1952, Overholt, Walker and Woods[8] called attention to hidden bronchiectasis in the asthmatic.

Selection of Cases

Intractable cases of asthma should have the benefit of a thorough investigation, particularly (1) those whose illness was initiated by an attack of pneumonia; (2) those who develop frequent colds which settle down in the chest; (3) those who have productive cough; (4) those who have a unilateral wheeze; (5) those who have chest discomfort or pain; and (6) those in whom there is systemic evidence of a focal infection, such as arthritis.

Whether or not patients who demonstrate no structural abnormality of the bronchial system be explored depends upon the degree of disability and the burden of the medical regime. At times, subjective or objective signs are present which attract attention to one side or the other. It may be a unilateral wheeze or localized discomfort or pain. Patients show an uncanny ability to lateralize their difficulty. With or without bronchographic

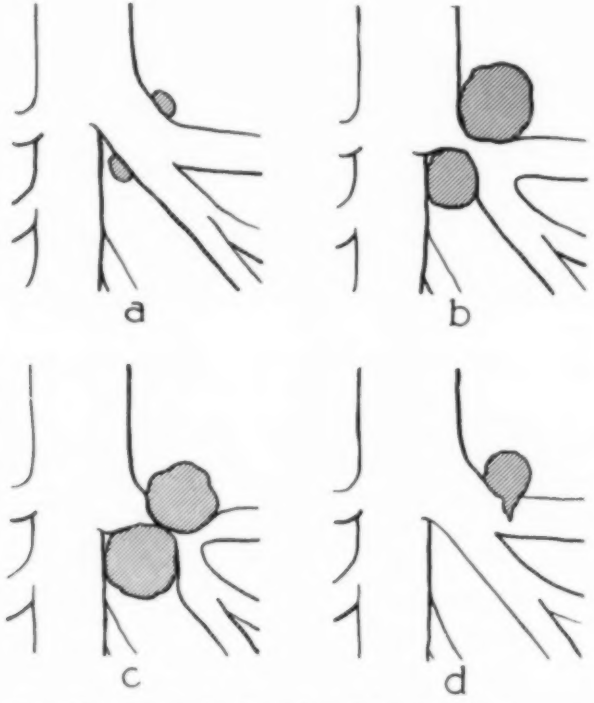

FIGURE 1: Bronchial compression by enlarged lymph nodes is a common trigger mechanism in asthma. (a) Relation of normal lymph nodes. (b) Partial occlusion. (c) Complete occlusion. (d) Perforating calcific node with spicule.

indication of abnormality, there may be strong presumptive evidence of mechanical difficulty which may be discovered at exploration and can be corrected forthwith.

Bronchography Safe and Essential

Although routine chest films are indicated in all individuals, normal lung fields will be found in most asthmatics. Visualization with contrast media is necessary if the presence, nature and extent of a structural abnormality in the bronchial system are to be determined. Since asthma has been considered by many to contraindicate bronchography, it seemed important to set forth a plan of management which minimizes risk:

1. *Preparation*—Patients are hospitalized for intensive medical management which usually includes intravenous aminophyllin drip, intermittent positive pressure breathing, aerosols and specific antibiotics, if indicated. Bronchography is deferred until maximum improvement of bronchospasm is effected.

2. *Technique*—This should be simple and free of all instrumentation save a single catheter. Preliminary sedation with a barbiturate and atrophine protects against topical anesthetic reactions.* After spraying the pharynx with the anesthetic solution, a catheter is passed via the nose into the posterior pharynx. With the tongue held forward, the patient is asked to cough and, as the epiglottis rises with the blast of air, the tube is given a quick thrust. Its tip passes into the trachea, and the distal end is fastened to the nose and forehead with adhesive tape. The trachea and bronchi are anesthetized by dripping the anesthetic solution through the catheter. With the patient under the fluoroscope, the contrast media is then instilled. The catheter is left in place until the films are developed and studied. If any area has been inadequately filled, the specific region under question is re-injected.

*An anesthetist accompanies the surgeon and patient to the x-ray department. Equipment for emergency intubation, oxygenation and control of respiration is always in readiness.

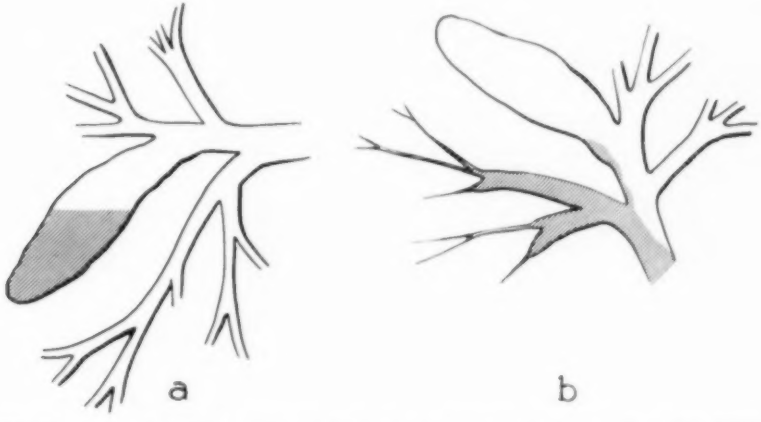

FIGURE 2: (a) A dilated bronchus acts as a collecting reservoir of liquid material (b) Altered position of reservoir causes flooding of other bronchi. Such irritation and blockage induce bronchospasm.

3. *Interpretation*—Structural abnormality is clearly indicated if saccular or tubular dilatation, incomplete stenosis, distortion, crowding or abnormal spread of branches are found. Evidence of non- or mal-function, without ectasia, is frequently less clear-cut. A segmental or subsegmental branch may fill and be of normal diameter, but be barren of finer branches. This lack of bronchiolar filling gives a "dead branch" effect in contrast to normal segments which show all the twigs. In delayed filling, functioning segments permit the media to pass on out into alveoli to produce "foliage." The barren or "dead-branch" segment never shows alveolarization in late films. Complete lack of filling of a segment means one of four things: (a) technical failure; (b) localized bronchospasm; (c) mucous plug; or (d) structural abnormality. Careful preparation, unhurried instillation with proper positioning and serial films will greatly reduce the likelihood of the first three possibilities. If conditions are right and a re-injection of a nonfilling segment again fails, the presence of an organic obstruction should be seriously considered.

What is Accomplished at Exploration

The study of the integrity and behavior of all segments is the first accomplishment of exploration. Proper examination requires an adequate exposure of a completely mobilized lung. It should be carefully inspected and palpated and its response to alterations in intrabronchial pressure tested. Variations in pigmentation are noted. In adults, the lymphatics will be laden with carbon particles in the segments which have been capable of ventilation. Nonfunctioning segments are usually devoid of pigment. The majority of the unpigmented areas trap air and remain inflated during the period of manipulation. Occasionally, an indurated,

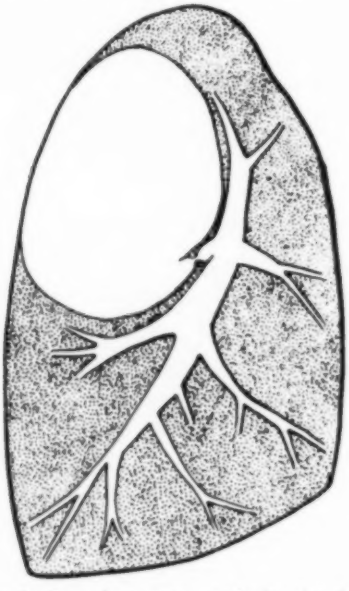

FIGURE 3: Check-valve in bronchus may result in the formation of a cyst which compresses, distorts and irritates bronchi.

contracted, atelectatic segment will be found which is free of pigment. Such a segment probably has been defunctionalized since childhood.

Variations in segmental density can be determined quite accurately by palpation. Bronchiectatic segments in which there has been chronic infection may show areas of contraction, thickening or nodulation. Enlarged lymph nodes and calcific deposits can be removed. The mediastinal pleura should be opened to facilitate inspection and palpation of that area. The esophagus is inspected and palpated under the azygos vein on the right or under the aorta on the left. Fibrotic, calcific or enlarged lymph nodes wedged between the esophagus and major bronchi are removed.

The compliance of the lung to pressure changes in the closed anesthetic system is the most important of all observations the surgeon makes. When the bronchi are in spasm, the lung builds up a volume greater than that of the hemithorax. It bulges out beyond the limits of the retracted chest wall, even though pressure is not maintained within the anesthetic system.*

*It is important that the anesthetist aspirate bronchial secretions and that the intratracheal tube be in satisfactory position. A bronchodilator drug, given intravenously, may temporarily release the spasm.

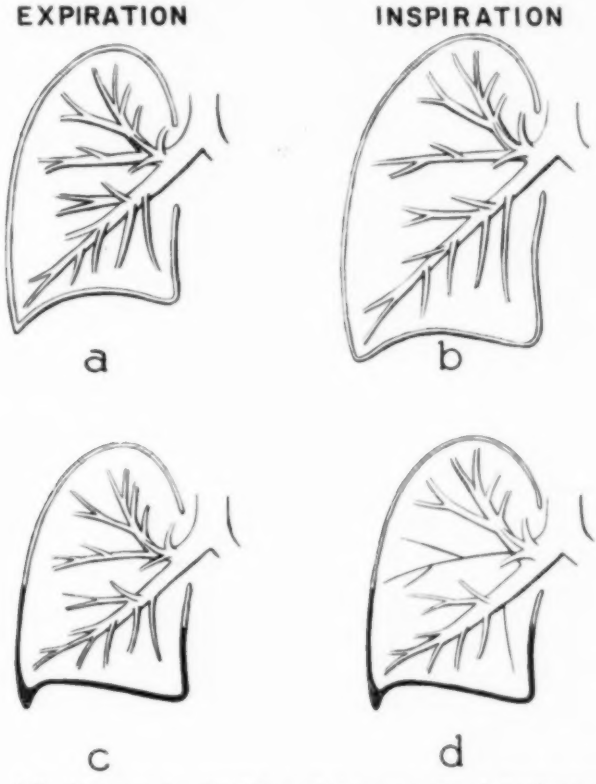

FIGURE 4: Adhesions may be situated so that movements of diaphragm or rib cage result in distortion or abnormal stress of bronchi. (a) Normal expiration. (b) Normal inspiration. (c) Anchorage of lung by adhesions during expiration. (d) Same during inspiration with abnormal stress on lung and its root. Note diminished caliber of bronchi in spasm.

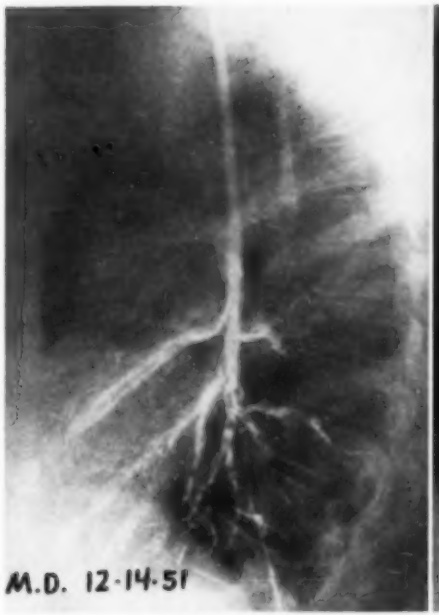

FIGURE 5

FIGURE 6

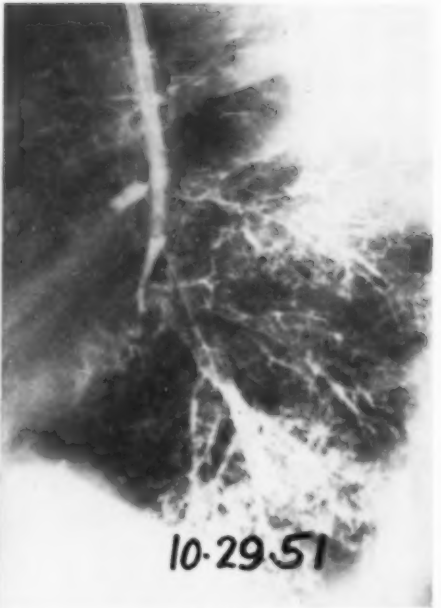

FIGURE 7

Figure 5: Right lateral bronchogram in severe asthmatic in whom enlarged nodes partially constricted middle-lobe bronchus. Attacks of asthma ceased after these nodes were removed.—*Figure 6:* Right lateral bronchogram in severe asthmatic which was done without adequate preparation. Only some of major bronchi are outlined.—*Figure 7:* Same case as Figure 6 after intensive medical preparation. Note satisfactory delineation of all segments except the right middle lobe and the anterior basal segment. These trigger mechanisms were removed. The patient has been free of asthma for the past seven years.

This situation provides an opportunity to test the effect of denervation. The vagus nerve is in full view and all branches entering the hilum can be readily divided, care being taken, if working on the left side, to avoid the recurrent nerve. Loose areolar tissue around the great vessels and major bronchi is divided and these structures virtually cleaned so they stand out separately. Major bronchial arteries are ligated and divided. In some cases, the healthy segments will immediately and uniformly deflate. In most, there will still be evidence of delayed or incomplete deflation and greater-than-normal pressure will be required to re-inflate. Diseased and functionless segments, obviously, are not influenced by the denervation. The next step is to interrupt the parasympathetic pathways. This also is easily accomplished as the sympathetic chain is in full view. The upper ganglia (T1-5) and the connecting trunk are removed. It is not necessary to disturb the stellate ganglia, thus avoiding a Horner's Syndrome. Following the double denervation, there is usually a dramatic change in the behavior of the lung. Healthy segments then readily comply to pressure variations as found in non-asthmatic individuals.

The final accomplishment of the exploration is concerned with the necessity for and extent of tissue excision. All bronchiectatic segments which are dependent and which act as collecting reservoirs or serve as a site for inflammation should be removed. The necessity for resection of such reservoirs is usually determined in advance by bronchography. The precise extent of structural abnormality and the number of functionless segments is settled at the time of exploration. Cystic areas which trap air and do not ventilate are not only useless, but interfere with the function of healthy segments. They either compress or trigger off spasm in adjoining segments.

In general, then, the surgeon inspects and overhauls the defective or abnormally functioning ventilatory organ. He liberates abnormally anchored segments, divides adhesions or bands, decorticates constricted segments, removes enlarged nodes or destroyed segments, denervates a spastic lung and works with it until all healthy segments are functioning properly.

Benefits

The value of exploration and the elimination of "trigger mechanisms" can best be told by summarizing the history of three illustrative cases and reporting on long-term follow-up studies. The first individual case report will indicate the severity and disabling nature of the disease for which bilateral surgery was required. In the second case, the "trigger" was abolished without sacrificing any pulmonary tissue. In the third, an unsuspected "trigger" was discovered at exploration and easily corrected.

Case Reports

Case 1: Mrs. H. B. This 33 year old married mother had been tortured by sudden, severe, long-standing attacks of status asthmaticus for 2½ years. These facts were in the medical record:

1. She had been under the care of eight different doctors, two eminent allergists and a hematologist.

2. There had been repeated admissions to hospitals in New York City and Boston during periods of a few days to several weeks. She was thoroughly studied from an

allergic standpoint and treated by desensitization, courses of antibiotics and prolonged steroid therapy. A muscle biopsy revealed periarteritis nodosa.

3. Upon 12 occasions, her husband had been summoned to the hospital and told that she was moribund and not expected to live through the night.

4. Her annual drug bill averaged $1600—not including those used during hospitalization periods.

On April 8, 1958, the right middle and lower lobes which were extensively involved with bronchiectasis were removed. The upper lobes inflated and deflated normally; therefore, a denervation of that lobe was considered unnecessary. She was discharged on the 15th post-operative day as improved. Wheezing was then limited to the unoperated (left) side. In May, 1952, she was rehospitalized for 19 days. She was in status asthmaticus, and a bronchoscopic aspiration was carried out under ether anesthesia.

On December 31, 1952, the left chest was explored, and the anteromedial basal segments of the lower lobe plus the lingula were resected. The remaining segments "trapped air" so a neurectomy and upper sympathectomy were done. She was discharged on the 13th post-operative day as considerably improved.

Follow-up—She has remained under medical supervision during the intervening 5½ years. There has been no serious episode requiring hospitalization. Her physician, Dr. Jerome Leff of Springfield, Massachusetts, writes: "Aside from her dependence upon a systematic schedule of ACTH, 80 units every 10-14 days, she seems in excellent physical health. She now weighs 103 pounds as against the 85 pounds she weighed when you operated upon her. She is active in professional modeling on and off television and is in addition a typical young housewife and mother who cares for a home, two young sons and a husband."

Case 2: Miss M. C. B. Age 45. Teacher. For six years, the patient had been having cough and wheezing. She had been treated with ACTH, KI and Tedral. She was studied in a university hospital a year previously for extreme shortness of breath. She was treated with nasal oxygen and intravenous medication of aminophyllin and hydrocortisone. She produced a glary mucus which she thought came from the right side. Occasionally, she experienced soreness in the right lower anterior chest. She had been tested for numerous allergies and none was found. She had never smoked. X-ray film was negative except for several small calcified areas in the right hilar region. The bronchial pattern was normal except for absence of bronchiolar filling of the two segments of the right middle lobe.

At exploration on November 27, 1957, the upper and middle lobes "trapped air." Pigmentation was evenly distributed. Calcified lymph nodes were found medial to the intermediate bronchus and were impinged between the take-off of the middle lobe and the anterior basal segmental bronchi. Vagal nerve branches were divided and all hilar and infracarinal nodes were excised, and an upper sympathectomy carried out. Then all segments inflated and deflated without undue delay. No resection was required.

Follow-up—In May, 1958, she reported continued progress with improved breathing, freedom from cough and wheeze, and she was carrying a full schedule.

Case 3: Mrs. A. S. Age 53. This lady's presenting symptom was intermittent pain in the right lower anterior chest of three years' duration. She had been treated medically for duodenal ulcer, and the gall bladder had been removed. She had also been under treatment for asthma for a 14-year period in three leading Boston hospitals. She was referred for surgery because x-ray films revealed a rounded mass in the right lower anterior chest, thought to be either a tumor or a diaphragmatic hernia through the foramen of Morgagni. The area of density so clearly called for exploration that bronchography was deemed unnecessary. Upon surgical exploration on April 17, 1958, the mass proved to be a localized eventration of the diaphragm for which no correction was necessary. Unexpectedly, a small, indurated, airless middle lobe was found. There were no adhesions. The other two lobes were normal. Right middle lobectomy was performed. The pain, cough, wheezing and dyspnea were relieved

TABLE I

BENEFITS IN 12 PATIENTS—DENERVATION ONLY

	Unilat.	Bilat.
Worse	0	0
Same	2	0
Better—Reduced Medication	2	1
Better—Occ. Medication	5	1
Better—No Medication—Well	1	0

TABLE II
BENEFITS IN 43 PATIENTS

	R + D	D Only
Worse	0	0
Same	0	2
Better—Reduced Medication	6	3
Better—Occ. Medication	10	6
Better—No Medication—Well	15	1

immediately. She was discharged on the 13th post-operative day. She has remained well and states that now for the first time in many years she appreciates the meaning of the term, "good health."

Long-Term Results

In a previous report,[9] the late results on 43 long-term surviving severe asthmatics treated surgically between the years 1945 and 1956, were given.* This report was concerned principally with an appraisal of vagal and sympathetic denervation either with or without excision of pulmonary tissue. There were 12 patients treated by denervation alone and re-appraised. Some degree of improvement was noted in 10 (Table I).

In appraising benefits, patients were re-examined and statements from both patients and their physicians were solicited. Improvement was undisputed or their condition was classified as the same. In the tabulation of the degree of benefit, it seemed expedient to group them, as follows:

1. Improved patients who required medication, but in reduced amounts. The majority in this group required some medical supervision.

2. Considerably improved patients who, on occasions, may medicate themselves. They rarely called upon a physician.

3. Those in whom asthmatic seizures have been eliminated. They enthusiastically reported that they were well.

Results were better in those in whom functionless segments were found and removed (Table II). There were 31 patients followed for periods of 18 months to 12 years.** All were improved to some degree, and three fourths of them significantly, as 25 of the 31 fall into Group 2 or 3. One half of the entire number treated were considered to be well and completely free of asthma.

SUMMARY

1. Intractable asthma may be perpetuated by structural abnormalities in bronchopulmonary segments which act as "trigger mechanisms."

2. Bronchography, if carefully done, is safe and often productive of useful circumstantial information necessary for successful management.

3. Surgical exploration permits direct inspection of the lung and testing of segments as to inflow and egress of air. Mechanical defects can be corrected forthwith and sympathetic, parasympathetic or both denervations carried out simultaneously.

*During this same period, 257 non-surgical cases of asthma were examined. The series of surgically treated asthmatics comprised 15 per cent of this number. Also, 1292 cases of bronchiectasis were seen. The patients having both bronchiectasis and surgically treated asthma represented 4 per cent of the total number of bronchiectasis cases seen in the 11-year period.

**There was no hospital death among the patients treated by resection plus denervation.

RESUMEN

1. El asma intratable puede ser perpetuada por anormalidades estructurales en los segmentos broncopulmonares que actúan como mecanismos desencadenentes.

2. La broncografía si se hace con cuidado, es segura y a menudo capaz de dar información circunstancial necesaria para un tratamiento con éxito.

3. La exploración quirúrgica permite la inspección directa del pulmón y probar los segmentos en cuanto al ingreso y egreso de aire. Los defectos mecánicos pueden ser corregidos, las denervaciones simpática, parasimpática o ambas, llevarse a cabo simultáneamente.

RESUME

1. Un asthme incoercible peut être entretenu par des anomalies de structure dans les segments bronchopulmonaires, qui agissent comme "mécanismes à barillet."

2. La bronchographie, si elle est soigneusement faite, est sans danger, et permet souvent de recueillir des renseignements précieux indispensables pour une bonne conduite du traitement.

3. L'exploration chirurgicale permet l'inspection directe du poumon et des segments pour vérifier l'entrée et la sortie de l'air. Des altérations mécaniques peuvent être corrigées immédiatement par énervations sympathiques ou parasympathiques ou les deux, pratiquées simultanément.

ZUSAMMENFASSUNG

1. Ein unbeeinflussbares Asthma kann verewigen als Ausdruck strucktureller Abnormalitäten in bronchopulmonalen Segmenten, die die Rolle von "Auslöse-Mechanismen" spielen.

2. Eine sorgfältig vorgenommene Bronchographie ist ungefährlich und oft von Wert als nützliche und eingehende Information, die notwendig ist für eine erfolgreiche Behandlung.

3. Untersuchung auf chirurgischem Wege gestattet eine direkte Inspektion der Lunge und Prüfung der Segmente hinsichtlich der Luftzufuhr. Mechanische Defekte können sogleich korrigiert und zusammen mit der Denervation des Sympathikus, Parasympathikus oder beiden ausgeführt werden.

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Unreported Tuberculosis Revealed by Death Certificates: Its Frequency, Characteristics and Significance

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Many victims of tuberculosis do not complain of symptoms or consult a physician. Many who do seek medical aid are not properly examined and diagnosed. Some cases which are recognized and treated are not reported, through ignorance, neglect, or deliberate defiance of the law. Despite continually improving case finding and reporting, the number of new active cases reported annually is, therefore, only a fraction of the total incidence of the disease.

The number of reported cases of tuberculosis is, however, often cited as if it constituted the real frequency of the disease.[1] Although delay in the diagnosis of early tuberculosis is readily admitted, it has been implied that most cases are recognized before they die.[2] The high incidence of unreported tuberculosis revealed by death certificates, therefore, arouses astonishment and incredulity. Even when the high frequency of previously unreported cases among those dying is admitted, it has been questioned whether this represents their prevalence among the living.[3]

Tuberculosis disclosed only by death certificates, though less than 10 per cent of new cases reported, exceeds a quarter of all deaths from this disease in the United States.[4] This does not include all cases not previously reported, since morbidity cards made out after the death by physicians, hospitals or other informants are often attributed to them, instead, and reports originating in the coroners or local clerical offices are sometimes assigned to the physicians whose names appear on the death certificates.

The number of previously unreported cases of tuberculosis revealed by death certificates varies greatly in different states (Table I). This is due to differences in local policies in recording and tabulation as well as to variations in the efficacy of case finding and other control measures. It is, accordingly, not regularly related to the total number of new cases reported, the number of deaths from the disease, the case-death ratio, or the geographical, economic or social characteristics of the states.

In some states the majority of all tuberculosis deaths had been previously unreported, while in others, the incidence of new cases ascribed to death certificates has been consistently low. In some other countries, the proportion of previously unreported tuberculosis revealed by death certificates has been somewhat less than in the United States[5] while in other places it has been much higher. Everywhere it is apparent that a large proportion of the communicable cases of tuberculosis are still unrecognized.

The reporting of tuberculosis has been compulsory in California for nearly half a century.[6] Tuberculosis case finding and reporting in this state is better than average. More than a million survey films are taken every year and nearly eight new cases are reported annually for each

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TABLE I
TUBERCULOSIS REPORTING IN THE UNITED STATES 1953

State	Tuberculosis Death Rate	Case Rate	% Reported only by Death Certificate
Arizona	29	163	68
Dist. Columbia	20	140	33
Tennessee	20	66	26
Kentucky	19	75	37
Arkansas	18	66	22
Alabama	17	37	21
Maryland	16	68	33
New Mexico	16	110	54
Nevada	15	65	37
Missouri	15	51	34
Pennsylvania	14	47	
Virginia	14	67	63
Delaware	14	58	15
Mississippi	14	53	29
Louisiana	14	55	49
West Virginia	14	53	23
Illinois	13	52	34
New Jersey	13	44	26*
New York	13	74	23
Texas	12	39	15
Montana	12	36	28
South Carolina	12	40	15
Ohio	12	59	28
Georgia	12	52	32
Colorado	11	36	59
Vermont	11	36	9
California	11	66	29
Massachusetts	11	45	24
Oklahoma	11	52	39
Rhode Island	10	39	19
South Dakota	10	24	58
Maine	10	40	22
Connecticut	9	36	3
North Carolina	9	35	10
Indiana	9	38	47
Florida	9	54	23
Michigan	8	54	12
Minnesota	6	27	19
Oregon	6	33	41
Washington	6	59	45
New Hampshire	6	25	32
Wisconsin	6	29	27
Nebraska	5	19	40
Utah	5	16	46
North Dakota	5	34	55
Kansas	4	18	34
Idaho	4	17	10
Iowa	4	17	31
Wyoming	3	22	41
United States	12	52	25

Compiled from *Reported Tuberculosis Morbidity* and other data Calendar year 1953. U.S.P.H.S. Publication no. 442 (4).
*1951.

death from tuberculosis.[7] Among those who do die of tuberculosis after their disease has been reported, the proportion succumbing in less than a year has diminished from more than 50 per cent to less than 25 per cent in the past decade.[8]

Nevertheless, the majority of the cases of tuberculosis in California have probably never been reported or even diagnosed. Less than 350,000 cases of active tuberculosis have been reported in California since 1912. Half of these have already died of the disease and many others have died of other causes or left the state. Less than 1 per cent of the present population of over 14 million, accordingly, could have been previously reported to have the disease in this state. Mass x-ray film surveys reveal previously unrecognized tuberculous lesions in another 1 or 2 per cent of apparently healthy adults, about a tenth of which are found to be active at the time.

At the average age at death, however, according to tuberculin test surveys, the majority of the population had been already infected by the tubercle bacillus. Gross tuberculous lesions, active or inactive, were diagnosed in more than 15 per cent of the autopsies performed in the Los Angeles General Hospital during this time.[9] Even among the persons in whom tuberculosis was the primary cause of death in California during the past decade, more than a third had never been previously reported to have the disease.

In order to compare the frequency, characteristics and significance of the fatal cases of tuberculosis which had been previously reported with those which had not, all death certificates in which tuberculosis was mentioned in California in 1953 were checked against an alphabetical index of all cases which had been reported from 1927 to 1954. Failure to find morbidity reports which had actually been made occurred in a few instances through clerical or filing errors. Cases which had been reported more than 25 years before or in another state, or under another name, were also missed. Mistakes in the opposite direction resulted from confusion of a reported case with someone else with a similar name who died of tuberculosis. Review of the work done, and independent check of other records in the Los Angeles County Hospital and in the Los Angeles County Health Department indicates that such errors occurred but were not frequent.

No previous morbidity report card was found for 34 per cent of the 1317 death certificates reporting tuberculosis as the primary cause of death. Among the 574 cases in which autopsies had been performed, 44 per cent had not been previously reported, as compared with 27 per cent of the 743 who had not been autopsied. About a third of the previously unreported cases, accordingly, probably represented undiagnosed tuberculosis not discovered until autopsy. These were active tuberculous lesions considered to be the primary cause of death, and not unimportant or incidental autopsy findings. More extensive autopsy examinations might have revealed other deaths from tuberculosis mistakenly attributed to heart and other diseases, but this number would be compensated in part by erroneous diagnoses of fatal tuberculosis in persons who had actually died of other causes.[10]

Proportionately fewer females had been autopsied, but more of them had not been previously reported as compared with the males. There were

more previously unrecognized cases among those under 15 years of age due to miliary and meningeal lesions which are often unrecognizable until near death, and also owing to the higher frequency of autopsies (61 per cent) in children. Most of the previously unrecognized cases, however, were in those over 65 years old despite the lower autopsy rate (39 per cent) among them (Table II). There was relatively more previously unreported tuberculosis among housewives, retired persons and those not working or of unknown occupations.

In spite of the higher incidence of autopsies among them, only 24 per cent of the veterans of the armed forces who died of tuberculosis had not been reported before death, but even this number is regrettable. Persons of foreign birth, non-citizens, chiefly Mexicans, and non-white races had more previously unreported disease than the American born Caucasians. This is partly accounted for by the higher incidence of acute forms of tuberculosis among them. The frequency of previously unreported tuberculosis in persons born in other states was no higher than that of the native sons. Less than 2 per cent of the death certificates were noted as non-residents of California. The reasons for unreported tuberculosis in California, accordingly, must be sought within the state borders.

TABLE II
FATAL TUBERCULOSIS IN CALIFORNIA DEATH CERTIFICATES IN 1953
PERSONAL DATA

	Total	Not Previously Reported	Per Cent
Sex			
Male	1317	449	34
Female	974	319	32
	343	130	37
Age			
Under 15	46	25	54
15-44	347	97	28
45-64	544	166	31
65	400	161	40
Race			
White	940	302	32
Mexican	176	73	41
Negro	121	44	36
Others or not stated	86	30	37
Birthplace			
California	230	75	32
U.S.	748	238	32
Mexico and S.A.	116	49	42
Europe	156	58	37
Asia	67	29	42
Citizenship			
Non Citizen of U.S.	169	62	36
Occupation			
Skilled	506	175	35
Unskilled	277	92	33
Housewife	231	91	39
Not working or not stated	203	91	45
Social Security	514	190	36
Veteran	236	58	24

Less than a quarter of the deaths from tuberculosis occurred in the more than 5000 beds in sanatoria or other tuberculosis institutions. More than 90 per cent of these had been reported before death and most of the others had been admitted in a terminal condition. More than half of the deaths occurred in other hospitals, some in tuberculosis wards which comprise about 4000 beds for tuberculosis but many in general medical wards or other non-tuberculous services. It is here that the greatest number of deaths in previously unreported cases occurred, often soon after admission. The proportion previously unreported was even higher in those dying in private hospitals, rest homes and at home (Table III).

The great majority of previously unreported persons dying of tuberculosis did so at home or in general hospitals where the disease had not been diagnosed and the patients were not receiving specific treatment for the tuberculosis. Unreported cases constituted 60 per cent of the 185 death certificates signed by the coroner or his deputy, 34 per cent of the 843 signed by other physicians some of whom were on working tuberculosis services but were not recognized tuberculosis specialists, but only 12 per cent of the 289 were signed by tuberculosis specialists. Admission X-ray films of all hospital admissions and more frequent consultation with tuberculosis specialists might have facilitated detection and reporting of some of these cases, but many came to the hospital in a terminal condition.

One quarter of the previously unreported tuberculosis deaths were signed out by the coroner, another quarter had been cared for by the physician signing the death certificate for less than one week, and another fifth for less than a month. About a third of the remainder had been cared for, usually for another condition, as in a mental hospital, for five years or

TABLE III

FATAL TUBERCULOSIS IN CALIFORNIA DEATH CERTIFICATES IN 1953
CIRCUMSTANCES OF DEATH

	Total	Not Previously Reported	Per Cent
Place			
Sanatorium	309	29	9
Hospital	818	328	39
Home	189	92	50
Certificate Signer			
Coroner	185	110	60
TB Specialist	289	46	12
Other	843	293	34
Autopsy			
Performed	574	253	44
Not Performed	743	196	27
Duration Attendance			
None	195	117	60
Under 1 month	461	212	44
1 to 12 months	342	75	22
1 year —	319	45	14
Duration Disease			
Under 1 year	110	48	44
1 to 5 years	232	31	13
Over 5 years	257	42	16
Not stated	728	328	45

more. The duration of the disease, reported on half of the death certificates, averaged nearly five years, and was usually longer than the period of care, especially for the patients whose disease had not been previously reported, and for the older patients. More than half of the cases reported to have survived less than a month from onset, mostly instances of tuberculous meningitis, had not been reported before death, as compared with less than 15 per cent of those which were estimated to have lasted for more than a year.

Only about a quarter of the death certificates for persons dying from tuberculosis who had not been previously reported, were signed by physicians who had cared for the patient for more than a month, and only about a tenth for more than a year. In most cases, then, the physician signing the death certificate had not had much opportunity to make the diagnosis and report it before the patient died. Some of these patients may have been cared for previously by some other physician, who had missed the diagnosis or had failed to report it. Examination of the records of persons who died of previously unreported tuberculosis at the Los Angeles County Hospital, as well as direct communication with the last attending physician in a previous series of such cases in Los Angeles, however, indicated that the majority of these patients had not been treated for tuberculosis by anyone.

Terminal mechanisms or fatal complications, recorded in more than half of the death certificates, showed striking differences in distribution between these whose tuberculosis had been previously recognized and reported, and those in which it had not. Pulmonary heart disease or corpulmonale, fatal hemorrhage from the lung, and complications of surgery or pneumotherapy accounted for nearly two thirds of the deaths in previously reported cases, but in only one third of the deaths in persons whose tuberculosis had not been reported. Miliary or meningeal tuberculosis, extrapulmonary tuberculosis, and inanition, which often result from tuberculous enteritis or laryngitis, accounted for two thirds of the deaths in previously unreported cases, and in only one third of those previously reported. Most of the persons whose tuberculosis had not been previously

TABLE IV

FATAL TUBERCULOSIS IN CALIFORNIA DEATH CERTIFICATES IN 1953 DIAGNOSIS

	Total	Not Previously Reported	Per Cent
Form of Tuberculosis			
Pulmonary, Active or not stated	1109	327	30
Pulmonary, Inactive	19	7	37
Extrapulmonary	189	115	61
Terminal Mechanism or Complication			
Cor Pulmonale	122	30	24
Hemorrhage	109	29	26
Operation	71	19	26
Pneumothorax	36	8	22
Fibrosis or Pulm. Insufficiency	37	8	21
Inanition	116	50	57
Meningitis	116	70	60
Other Extrapulmonary Tuberculosis	47	28	59
No information given	663	207	32

reported and in whom the mechanism of death was indicated succumbed to tuberculous complications which are generally amenable to modern chemotherapy (Table IV).

The 1317 death certificates in which tuberculosis was recorded as the primary cause of death included the fatal complications or sequelae such as operative shock, cor-pulmonale, or pulmonary fibrosis. In another 533 death certificates tuberculosis was listed as a contributory factor in death caused by some entirely different condition which was fatally aggravated by the reduction in pulmonary or other vital reserve resulting from it. These included some patients dying of arteriosclerotic heart disease or other disease with unrelated tuberculosis which had been previously diagnosed or revealed at autopsy, whether progressing, active, inactive or "healed."

The cases in which tuberculosis was merely a contributory cause of death included a higher proportion of males, whites, older ages, skilled workers and veterans, and the disease had not been previously reported in half of them, as compared with only a third in which it was the primary cause of death. There was also more previously unreported disease among females, older persons, foreign-born and unemployed who died primarily of other causes (Table V). Fewer of them had died in sanatoria or under the care of tuberculosis physicians or had been under treatment for a long time,

TABLE V
CONTRIBUTORY TUBERCULOSIS IN CALIFORNIA DEATH CERTIFICATES IN 1953
PERSONAL DATA

	Total	Not Previously Reported	Per Cent
Total	533	253	49
Sex			
Male	422	196	46
Female	111	57	51
Age			
-15	6	3	50
15-	50	18	36
45	241	97	40
65-	235	135	52
Race			
White	452	221	48
Mexican	39	20	51
Negro	23	5	46
Other	19	7	37
Birthplace			
California	83	30	36
U.S.	310	148	47
Mexico & S.A.	36	20	55
Europe	86	49	57
Asia	19	6	33
Occupation			
Skilled	271	107	40
Unskilled	112	60	53
Housewife	85	47	55
Not working	65	39	60
Social security	251	154	61
Veteran	102	40	39
Non Citizen	68	33	48

but in those who had the tuberculosis was much more often previously reported (Table VI).

Most of the 74 instances in which tuberculosis was recorded as inactive had been previously reported, but the majority of the 26 extrapulmonary cases had not. The tuberculosis had been previously reported in three fourths of the 88 cases who died of an associated neoplastic disease, a third of these being bronchogenic carcinoma (Table VII).

Discussion

A large proportion of all persons dying from tuberculosis had not been previously reported to suffer from the disease. A still higher proportion of those dying from some other disease in whom tuberculosis was a contributing factor had not been previously reported. Tuberculosis of limited extent and favorable course is even more apt to be missed. Accordingly, it appears that the majority of all cases of active tuberculosis are never diagnosed. Since even among those whose disease had been reported, a large proportion are at home without treatment[11] the majority of sufferers from tuberculosis are not yet benefiting from the effective treatments now available.[12]

TABLE VI
CONTRIBUTORY TUBERCULOSIS IN
CALIFORNIA DEATH CERTIFICATES IN 1953
CIRCUMSTANCES OF DEATH

	Total	Not Previously Reported	Per Cent
Place of Death			
Sanatorium	74	11	15
Hospital	362	184	50
Home	97	58	60
Signed Certificate			
Coroner	76	43	56
TB Specialist	73	9	12
Other physicians	275	93	33
Autopsy performed	260	122	47
Not performed	273	131	48
Duration Attendance			
None or not stated	186	152	81
-1 month	154	69	44
1-11 months	117	19	16
1 year	76	13	16
Duration Disease			
-1 year	15	3	20
1-5 years	63	7	11
5 years	66	17	25
Not stated	388	210	55

TABLE VII
CONTRIBUTORY TUBERCULOSIS
CALIFORNIA DEATH CERTIFICATES IN 1953
DIAGNOSIS

	Total	Not Previously Reported	Per Cent
Tuberculosis			
Pulmonary active or not specified	320	114	35
Inactive	74	10	13
Extrapulmonary	26	16	61
Cause of Death			
Resp. diseases	33	12	36
Circulatory	186	64	33
Neoplasm	88	23	26
Other	226	154	68

The difference between the fate of diagnosed and undiagnosed cases of tuberculosis is not definitely known. Even in the days when the diagnosis of tuberculosis was considered a death warrant, a majority of those with lesions demonstrable at autopsy died of other causes. Since then the prognosis of unrecognized tuberculosis has improved as a result of fewer and smaller reinfections, better nutrition, improved living conditions, and the decline in intercurrent diseases. Diagnosed cases may profit from better general care and non-specific treatment even if, as is often the case, they do not receive effective chemotherapy. The reported cases probably represent more extensive and readily detected lesions, so they may be expected to have a poorer initial prognosis. Thousands of patients annually still die in tuberculosis hospitals and sanatoria, despite the tuberculostatic drugs[13] and only too many of the known cases who are not in such institutions are not yet receiving these agents.[14]

Nevertheless, chemotherapy does save many tuberculous patients, who eventually succumb to other conditions, and prolongs the lives of many who do die of tuberculosis. With therapeutic improvements, the fatality rate among treated cases falls, until, with very effective treatment, few deaths may be expected among those so treated. Accordingly, the proportion of previously unreported, and hence untreated cases among those dying of tuberculosis may be expected to increase, even though, with better case finding and more energetic institutional and outpatient treatment programs, more and more of those with the disease may be saved.

The greatest number of new active cases may be found among groups with high tuberculosis rates, such as persons with suggestive symptoms, those previously treated for the disease, contacts of diagnosed vectors of the bacillus, general hospital admissions, prisoners, older individuals, males, members of nonwhite races, slum dwellers, and migrants from places of higher prevalence. Routine x-ray screening of such persons, with repeated examinations, and persistent follow up of all suspects are essentials for tuberculosis control.

Failure to seek and obtain adequate diagnosis in tuberculosis, however, is not restricted to any few elements in the population. Whether primarily fatal or merely a contributory cause of death, tuberculosis which had not been reported was found in all groups of the population. No sex, age, race, nativity, citizenship, veteran status, occupations, or apparent economic status was exempt from unreported disease. In both series, those with little or no medical care and those not seen by tuberculosis specialists were less apt to be reported. Community wide x-ray surveys, though expensive and relatively unproductive in themselves in places with effective tuberculosis programs, reveal some cases where least suspected. Tuberculin test surveys with investigation of young reactors and recent converters and their contacts reveal few new active lesions, in comparison with examinations of more frequently affected groups. They may, however, be important in uncovering otherwise unsuspected foci of infectious tuberculosis.

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Note: The 3200 California death certificates which mentioned tuberculosis from the years 1957 and 1958 were analyzed and yielded similar findings. In comparison with 1953 there was a larger percentage of autopsies, and the tuberculosis was more often only a contributory cause of death; accordingly there was a relative increase in those whose disease had not been previously reported. The analysis continued to show a higher proportion of previously unreported tuberculosis in women, the very young and the very old, non-whites, non-veterans, those dying at home or in general hospitals, and whose death certificates were signed by the coroner. Some previously unreported fatal tuberculosis, however, occurred in all age, sex, race, economic and social groupings.

Most of those whose tuberculosis had been previously reported succumbed to pulmonary fibrosis with cardiorespiratory insufficiency or cor-pulmonale. The majority of those whose disease had not been previously reported, however, died of progressive pneumonic or destructive pulmonary lesions or of extrapulmonary complications of tuberculosis.

SUMMARY

New tuberculous infections and cases of active disease, as well as deaths from tuberculosis are diminishing at an ever-accelerating rate. Too many such tragedies, however, still occur. Unrecognized far advanced active pulmonary tuberculosis constitutes the most dangerous source for spreading the bacilli. Until all open cases are found and placed under care, further new infections may be expected. The life saving benefits of the great advances in the treatment of tuberculosis made in recent years can only be realized when they are actually administered. Accordingly, tuberculosis progresses to death most often where it is not recognized and treated. Previously unreported cases of tuberculosis revealed by death certificates emphasize the frequency and dire consequences of such undiagnosed tuberculosis, and the importance of unremitting further efforts at finding and treating it.

RESUMEN

Los casos de infección nueva de tuberculosis y de tuberculosis activa así como las defunciones por la misma enfermedad, están disminuyendo en proporción siempre acelerada.

Sin embargo, aún ocurren demasiadas tragedias por la enfermedad. La tuberculosis no advertida, activa y muy avanzada es la fuente más peligrosa para diseminar el bacilo. Hasta que todos los casos abiertos se descubran y se traten, son de esperarse más infecciones. Los beneficios salvando vidas debidos a los grandes progresos en el tratamiento de la tuberculosis en los últimos años pueden obtenerse sólo si deveras se aplican. De acuerdo con 10 anterior, la marcha hacia la muerte en tuberculosis se ve entre los casos no reconocidos ni tratados. Los casos no reportados antes y sus consecuencias lamentables, según se ve por los certificados de defunción, hacen resaltar la importancia de continuar con esfuerzos sin descanso para hallar y tratar los casos.

RESUME

Les primo-infections tuberculeuses et les formes évolutives, aussi bien que les morts par tuberculose, sont en diminution, à un rythme croissant. Cependant, il existe encore trop de tradégies de cette catégorie. Lorsqu'elle n'est pas reconnue, la tuberculose pulmonaire évolutive grave constitue la source la plus dangereuse de dissémination des bacilles. Tant que les nouveaux cas contagieux ne seront pas tous découverts et mis sous surveiliance, on devra s'attendre à de nouvelles infections ultérieures. Les grands progrès du traitement de la tuberculose effectués ces dernières années ont permis de sauver des vies humaines mais à la seule condition qu'ils soient véritablement administrés. En conséquence, la tuberculose évolue le plus souvent vers la mort quand elle n'est pas découverte et traitée. Les cas de tuberculose qui n'ont pas été déclares antérieurement, et que permettent de découvrir les certificats de décès, montrent la fréquence at les terribles conséquences de ces cas de tuberculose occulte. Ellos démontrent aussi l'intérêt de ne pas abandonner dans l'avenir les efforts nécessaires pour les découvrir et les traiter.

ZUSAMMENFASSUNG

Neue tuberkulöse Infektionen und Fälle von aktiver Erkrankung ebenso wie Tod an Tuberkulose werden in immer zunehmendem Masse weniger. Es ereignen sich aber immer noch zu viele solcher Tragödien. Unerkannte, weit forgeschrittene, aktive Lungentuberkulosen stellen die gefährlichste Quelle für die Bazillenaussaat dar. Bis alle offenen Fälle gefunden und in Betreuung genommen sind, muss man mit weiteren neuen Infektionen rechnen. Die lebensrettenden Vorzüge der grossen Fortschritte in der Behandlung der Tuberkulose, die in den letzten Jahren gemacht wurden, können nur dann verwirklicht werden, wenn sie im Augenblick zur Anwendung gebracht werden. Dem entsprechend verläuft die Tuberkulose besonders häufig tödlich, wenn sie nicht erkannt und behandelt wird. Zuvor nicht gemeldete Tuberkulosefälle, die sich erst auf dem Totenschein ergeben, beleuchten die Häufigkeit und die schrecklichen Folgen einer solchen nicht erkannten Tuberkulose und die Wichtigkeit unablässiger weiterer Anstrengungen, sie aufzufinden und zu behandeln.

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"Cavitary" Lesions in Sarcoidosis*, **

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It is generally agreed that probably the first case of sarcoidosis was described by Hutchinson[1] in 1869. Subsequently he called the condition "Mortimer's malady."

Besnier[2] described a condition that he called "lupus pernio" in 1889 and Boeck[3] documented a cutaneous condition which he called cutaneous sarcoid in 1899. Then in 1917, Schaumann[4] integrated these clinical conditions into a single entity which he called benign lymphogranulomatosis. Since that time there has been a voluminous amount of literature upon various aspects of sarcoidosis. However, autopsy material has accumulated slowly. Rubin[5] estimated that in 1954 there were approximately 150 cases on record. The diagnoses, however, were uncertain in many of these cases and also in a number of cases the accounts were meager or confused by complicating factors such as tuberculosis.

In spite of this, much information has been gained about the pathology of sarcoidosis. However, the mechanisms involved in formation of cavities, bullae and ectatic bronchi have not been fully explored so far as we can ascertain from the literature. The purpose of this paper is to present three proven cases of sarcoidosis, uncomplicated by tuberculosis, which exhibited rarefactions on their chest films and to discuss the possible mechanisms involved in their pathogenesis.

Case Reports

Case 1: R. J., a 31 year old housewife, was first seen in the Chest Clinic of Freedmen's Hospital on April 23, 1953, with a complaint of wheezing and dyspnea. Her initial chest film had been taken on November 24, 1952 and sarcoidosis was suspected. There were bilateral wheezes heard on physical examination and the breath sounds were harsh. Bronchoscopy on June 18, 1953 was negative and a tuberculin test (.0002 PPD) on May 1, 1953 was negative.

In June, 1955, she noticed pedal edema which was progressive, also dyspnea and weakness. She was hospitalized on June 13, 1955, at which time she was orthopneic. Blood pressure was 96/65, pulse 124 per minute, P_2 was accentuated, venous pressure was 234 mm. H_2O with circulation time of 14 seconds. Pre-scalene node biopsy on February 5, 1954, was compatible with sarcoidosis.

The clinical diagnoses on admission were sarcoidosis and cor pulmonale. The patient failed to improve with digitalization, diuretics and steroid therapy and died on December 29, 1955. All sputums and bronchial washings had been negative for tubercle bacilli by smear and culture.

Her chest films are shown in Figures 1A, B, C and D. Figure 1D is a tomogram showing what appears to be a thick walled cavity in the right mid lung field. Figure 1C shows bilateral emphysematous bullae. The first two films, Figures 1A and B, show progression of disease from November 24, 1952 to March 19, 1954.

Autopsy was performed on December 30, 1955. There were numerous emphysematous bullae bilaterally of various sizes. In the apex of the lower lobe on the left there was a thick walled cavitary lesion measuring 3 x 4 cm. The normal lung parenchyma was widely replaced by fibrosis.

Case 2: E. T., a 30 year old woman, was admitted to this hospital on September 2, 1955, with the complaint of sudden shortness of breath and right chest pain. She

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had previously been hospitalized on the same service from August 14, 1952, to September 22, 1953, at which time the diagnosis was considered to be pulmonary tuberculosis, far advanced, active. This was on the basis of the x-ray film appearance and a positive skin test. During her hospitalization and subsequently she never had a positive sputum either by smear or culture.

On January 24, 1954, a cervical lymph node biopsy was performed. Microscopic examination was interpreted as being consistent with Boeck's sarcoidosis and in May, 1955, a tuberculin test was reported as being negative.

When admitted to the hospital on September 2, 1955, her x-ray film revealed the presence of 80 to 90 per cent collapse of the right lung. Closed thoracotomy suction was instituted without success. It was decided to operate for the purpose of closing

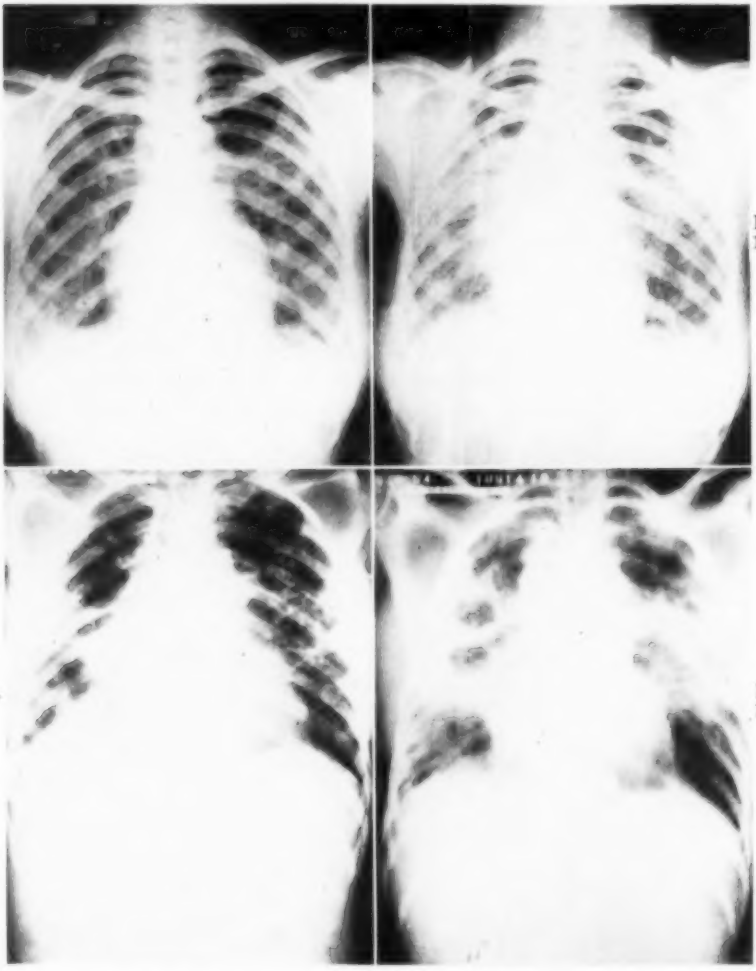

Fig. 1A

Fig. 1B

Fig. 1C

Fig. 1D

Figure 1A: Chest film on R. J. dated November 24, 1953, shows no obvious rarefactions and exhibits only bilateral pulmonary sarcoidosis with paratracheal and tracheobronchial lymphadenopathy.—B, Film taken March 10, 1954 shows the lesions are more dense and there are small rarefactions in the mid-lung zone and the left.—*C*, On the film of August 22, 1955, there are numerous bilateral rarefactions with poorly defined walls, small annular rarefactions in the left mid-lung zone, and a thick walled rarefaction in the right mid-lung zone.—*D*, Tomogram of December 16, 1954, at 7 cm. from posterior chest reveals a thick walled rarefaction at the fourth posterior rib level on the right.

any open rents in the lung parenchyma. At the time of operation, she developed a sudden shock-like picture with almost unobtainable blood pressure. Following administration of digitalis and meticorten, she improved to the point where surgery could again be attempted. On November 22, 1955, she underwent an exploratory thoracotomy on the right, at which time an apical pleurectomy with excision of hilar lymph nodes and imbrication of surface emphysematous blebs were performed. Following surgery, she had several bouts of hemoptysis. The expansion of the lung

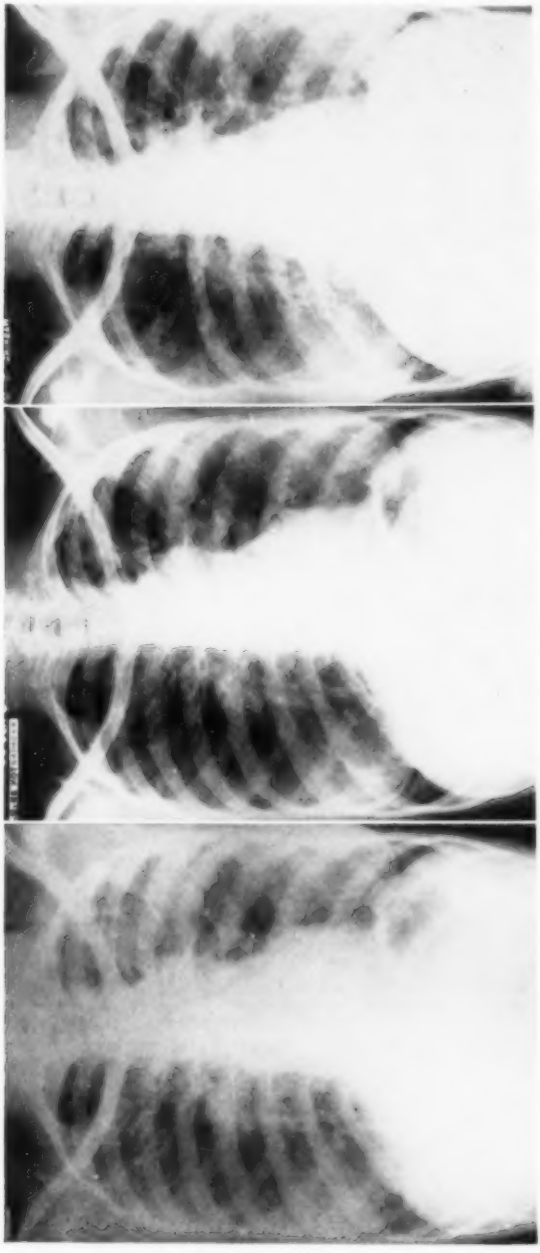

FIGURE 2A FIGURE 2B FIGURE 2C

Figure 2A: The film of May 10, 1955, shows dense fibrotic areas in the left upper chest and small blebs in the right upper chest.—*B*, On August 16, 1955, the dense fibrotic area on the left upper chest had shelled out leaving a thick walled cavity.—*C*, The large rarefaction on the left persists in November, 1956, *Figure 2A*: The film of May 10, 1955, shows small annular rarefactions near the left lung root which are suggestive of ectatic bronchi.

was maintained after drainage tubes were removed. Metacorten was discontinued. On observation the expansion was maintained and she was discharged as improved on January 18, 1956, with the following diagnoses:

1. Boeck's sarcoidosis
2. Acute cor pulmonale
3. Spontaneous pneumothorax re-expanded
4. Exploratory thoracotomy on the right with pleurectomy and imbrication of emphysematous blebs.

Since her discharge she has been periodically followed in our chest clinic except for a period of two months between August and September, 1956, during which time she had to be hospitalized in a local hospital because of hemoptysis.

Laboratory data had been within normal limits during the entire course of clinic and hospital follow-up. At present, she is asymptomatic except for some shortness of breath on exertion.

Pulmonary function studies performed on January 13, 1956, showed the following results:

	Actual	*Predicated*
Minute Volume Respiration	8.8 liters/min.	5.0 liters/min.
Maximum Breathing Capacity	37.7 liters/min.	80.6 liters/min.
Vital Capacity	1.1 liter	2.6 liters

The spirographic pattern was primarily restrictive rather than obstructive.
Arterial Saturation = 89.1 per cent.
Her chest films are shown in Figures 2A, B and C.

Case 3: C. W., a 41 year old electrician, was hospitalized on June 11, 1954, because of dyspnea, weight loss and swelling on the right side of the neck and in both armpits. Symptomatology had begun about one and a half years prior to admission. Four months before admission he had developed productive cough-lymph node biopsy in March, 1954, and was reported as compatible with sarcoidosis.

Past history revealed that he had been rejected for military service in 1954 because of hypertension. During childhood he was alleged to have had "soft bones" which interfered with his physical activity. The family history was not contributory.

Upon admission to the hospital, he was found to be well developed but poorly nourished and exhibited bilateral cervical and axillary lymphadenopathy. There was diminished tactile and vocal fremitus with diminished breath sounds over both lung fields anteriorly. Chest films showed bilateral cystic disease of the lung. There was reversal of the A/G ratio.

On this admission he was given nitrogen mustard for sarcoidosis and discharged on June 21, 1954. The second admission occurred on September 29, 1954 and on this

Results of Cardiorespiratory Studies

Spirography	*10-5-54 (Pre-op.)*	*1-6-55*	*4-26-55*
Minute Volume Rate	7,070 cc.	7,848 cc.	7,654 cc.
Minute Volume (Pred.)	6,288 cc.	6,480	6,300
Maximum Breathing Capacity	34,450	48,321	41,361
Maximum Breathing Capacity (Pred.)	102,623	117,180	113,925
Breathing Reserve per cent		40,473	33,707
Breathing Reserve %		83	83
Vital Capacity	1,551	1,924	1,417
Vital Capacity (Pred.)		4,500	4,375
Expiratory Capacity	280	411	277
Resting Ventilation	*10-8-54*		
Resting Ventilation	7.07 lit./min.	.09 lit./min./BSA	
O_2 Consumption	301.9 cc./min.	174.6 cc./min./BSA	
CO_2 Elimination	214.2 cc./min.	123.9 cc./min./BSA	
Ventilatory Equivalent	2.34		
Functional Residual Capacity	1,655		
Residual Capacity	1,375		
Total Capacity	2,926		
Residual Volume			
Total Capacity	47%		

occasion he received a resection of the basal segments of the left lower lobe with removal of a large emphysematous bulla. He was discharged November 7, 1954, as improved. On his third admission, April 20, 1955, he had right thoracotomy but resection was not done because of the extensive involvement of the lung with emphysematous bullae and he was discharged on June 11, 1955. The fourth admission, November 9, 1956, was because of pulmonary infection which responded to antibiotics. He was finally discharged on December 9, 1956.

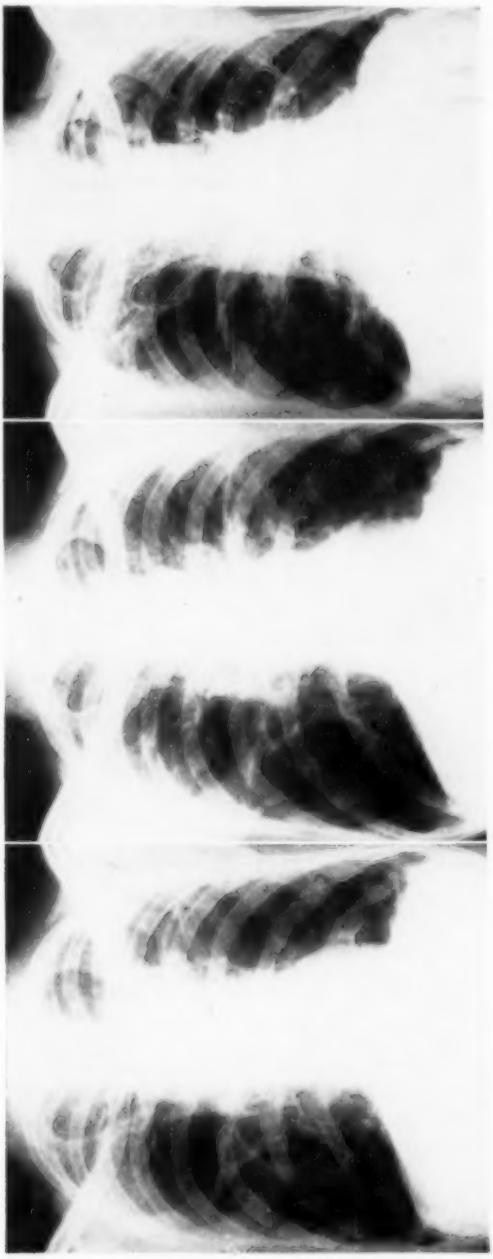

FIGURE 3A FIGURE 3B FIGURE 3C

Figures 3, A and B: Expiration and inspiration films on C. W., taken October 8, 1954, show bilateral bullae which fail to deflate on expiration, indicating an obstructive mechanisms.—*C*, Film of February 26, 1956, shows increase in size of bullae on the right. The left lower lobe has been removed. Patient experienced some relief of dyspnea following surgery.

He is currently being managed with bronchodilators and antibiotics. The large bilateral emphysematous bullae are shown in Figures 3A, B and C.

Pathological reports on the surgical specimen showed "marked fibrosis with an epitheloid tissue which is focally and diffusely infiltrated by chronic inflammatory cells. There are well defined tubercles." Impression: Probable Boeck's sarcoid.

The spirographic pattern was one of primarily obstructive disease with prolongation of expiration and air trapping.

Discussion

On the basis of a survey of the literature and our own experience, we submit that there are at least three types of pulmonary lesions occurring in sarcoidosis which appear as rarefactions on the chest x-ray film.

Type I: True Cavitary Lesions of Sarcoidosis. This type of lesion is exemplified in Case 1, R. J., as shown in her tomogram, Figure 1D, and also in her autopsy findings. Case 2, E. T., apparently exhibits this type of cavity in her left upper chest in Figures 2A, 2B and 2C which reveal an opacified area that subsequently develops into a rarefaction with well defined walls.

Tice and Sweany[7] in reporting an autopsied case of sarcoidosis described a thick-walled cavity which they did not characterize as either an ectatic bronchus or an emphysematous bulla. Ustvedt[8] reported necropsy findings in a patient with Heerfordt's syndrome, and who exhibited apical cavitation without tuberculous or sarcoid changes in the walls. Van Rijssel[9] believes that the expulsion of hyaline material may be responsible for the formation of these cavities and the sequence of events in Case 2, E. T., would seem to be compatible with this explanation.

One would expect a pattern of restrictive pulmonary insufficiency in pulmonary function tests when this type of cavity occurs in conjunction with hyalinized sclerotic lesions.

Type II: Emphysematous Bullae and Blebs. There were numerous bullae present in Case 1, as described in the autopsy findings and as in Figure 1C. Case 2 showed several bullae in the right upper chest. However, Case 3 showed large emphysematous bullae throughout both lungs and this was confirmed histologically in the surgically removed left upper lobe. The presence of bullae and blebs complicating sarcoidosis has been noted by many observers including Tice and Sweany,[7] Rubin,[5] and Loncope and Frieman.[10] However, there is a paucity of information concerning their formation other than that they are associated with the end stage fibrotic changes of sarcoidosis.

Schaumann[6] felt that obliterative changes in interlobular arteries led to ectatic changes in the alveoli which resulted in bullae of varying sizes. Spain,[11] however, in reporting the findings on a surgical specimen indicated that the emphysema and bullae present were undoubtedly secondary to bronchiolar involvement with the lesions of sarcoidosis. Turiaf[12] emphasized that bronchial biopsy may reveal the lesions of sarcoidosis even if they are not visualized on bronchoscopy. Longcope and Freiman,[10] Siltzback and Som,[13] and Turiaf and associates[12] have all noted bronchial and bronchiolar involvement. Coates and Comroe[14] found hyperinflation in five of eight cases of sarcoidosis receiving pulmonary function studies. They believed that the hyperinflation was primarily due to obstructive lesions rather than because of primary destruction of alveolar septa and loss of elasticity. Our Case 3 showed evidence of obstructive disease on pulmonary function studies.

We suggest that bronchial and bronchiolar involvement with the lesions of sarcoidosis may be a significant mechanism in the formation of emphysematous bullae. In cases where they are the predominant lesions, one would expect the obstructive pattern to be shown in pulmonary function studies.

Type III: Ectatic Bronchi and Bronchiectasis. This type of rarefaction is best exemplified in Case 2, Figure 2C, near the left lung root. Ectatic bronchi have been noted by Reisner,[15] Longcope and Freiman[10] and others. These may result from bronchial distortion due to pulmonary and peribronchial fibrosis or to superimposed infection. Characteristically these appear as small annular rarefactions. However, when cystic bronchiectasis is present the rarefactions are apt to be larger and the walls somewhat thinner. Pulmonary function studies may reveal restrictive or obstructive disease depending upon the state of the bronchial tree.

SUMMARY

1. Three cases of sarcoidosis exhibiting three types of rarefactions on their chest x-ray films are presented.

Type I: True Cavitary Lesions of Sarcoidosis which are characterized by well defined cavity walls and are probably formed by expulsion of hyalinized material.

Type II: Emphysematous Bullae and Blebs which have thin poorly defined walls. One mechanism of their formation may be due to the partial

obstruction caused by the lesions of sarcoidosis in the bronchi and bronchioles.

Type III: Ectatic Bronchi and Cystic Bronchiectasis. There are small annular and usually multiple rarefactions. Their formation is related to bronchial and bronchiolar distortion and infection.

2. The importance of bronchial biopsy and pulmonary function tests in sarcoidosis is emphasized.

RESUMEN

1. Se presentan tres casos de sarcoidosis que exhiben tres tipos de rarefacción en las radiografías.

Tipo I: Verdaderas lesiones cavitarias de sarcoidosis que se caracterizan por las paredes bien definidas y probablemente producidas por la expulsión de material hialinizado.

Tipo II: Bulas enfisematosas y ampollas con paredes delgadas mal definidas. Un mecanismo de su formación puede ser la obstrucción parcial causada por las lesiones de sarcoidosis en bronquios y bronquiolos.

Tipo III: Bronquiectasis quística y éxtasis bronquial. Estas son rarefacciones pequeñas, anulares y generalmente múltiples. Su formación está en relación con la distorsión bronquiolar y la infección.

2. Se recalca la importancia que tienen la biopsia bronquial y las pruebas funcionales pulmonares en el diagnóstico de la sarcoidosis.

RESUME

1. L'auteur présente trois cas de sarcoïdose montrant trois types de pertes de substance sur les clichés radiologiques du poumon.

Type I: Véritables lésions cavitaires de sarcoïdose, caractérisées par des parois cavitaires bien délimitées, et probablement formées par l'expulsion de substance hyaline.

Type II: Bulles d'emphysème, et vésicules qui ont des parois minces faiblement délimitées. Un des mécanismes de leur formation peut être imputable à l'obstruction partielle causée par les lésions de sarcoïdose dans les bronches et les bronchioles.

Type III: Bronches dilatées et bronchiectasie kystique. Ce sont de petites pertes de substance annulaires, et généralement multiples. Leur formation est en rapport avec la distorsion bronchique et bronchiolaire et l'infection.

2. L'auteur signale l'importance de la biopsie bronchique et des tests de la fonction pulmonaire dans la sarcoïdose.

ZUSAMMENFASSUNG

1. Bericht über 3 Fälle von Sarkoidosis, die 3 Typen von vermehrter Grundhelligkeit auf ihren Thoraxröntgenfilmen bieten.

Typ I: Echt kavitäre Herde der Sarkoidose, charakterisiert durch gut abgegrenzte Kavernenwände, die wahrscheinlich durch Ausstossung von hyalinisiertem Material entstanden sind.

Typ II: Emphysematöse Bulla und Bläschen, die dünne, schlecht abgegrenzte Wände haben. Ein Mechanismus ihrer Entstehung kann bedingt sein durch partielle Stenose als Folge von sarkoidomatösen Herden in den Bronchien und Bronchiolen.

Typ III: Ektatische Bronchien und cystische Bronchiektasie. Hier be-

stehen kleine ringförmige und gewöhnlich multiple Aufhellungen. Ihre Genese steht in Beziehung zu einer bronchialen und bronchiolären Distorsion und Infektion.

2. Es wird die Wichtigkeit der bronchialen Biopsie und Lungenfunktionsproben bei der Sarkoidose hervorgehoben.

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The Use of Steroids in Tuberculous Patients with Untoward Reactions to Anti-Microbial Therapy

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Introduction

The occurrence of untoward reactions in tuberculous patients receiving chemotherapy is not uncommon. Occasionally, these effects may be so severe or persistent as to jeopardize the continuation and successful administration of drug therapy. In such instances, the usual symptomatic therapy and anti-histaminic agents may be of no avail. The purpose of this study was: (1) To determine the efficacy of a regimen of combined steroid and chemotherapy, in patients exhibiting moderate to severe reactions to anti-tuberculous drugs; (2) to determine the effect of such therapy on the underlying tuberculous process.

Plan of Study

Cases were selected that had both active pulmonary tuberculosis and severe untoward drug reactions to one or more antimicrobial drugs. Baseline studies were obtained, namely, description of the drug reaction, extent of the pulmonary tuberculosis and estimates of liver, kidney and peripheral blood status. Then all chemotherapy was discontinued. Initially, steroid hormones were administered in suppressive doses for three days, ACTH—gel 80—120 units intramuscularly and, if necessary, prednisolone 10—15 units units t.i.d. Anti-histaminic medication (oral and/or parenteral) plus steroid ointment (locally) were used as supplements, if required. The severity of the reaction was the criterion used in estimating the dosage of steroid hormone to be employed. Following the initial three days of suppressive hormonal therapy, the anti-tuberculous agents were introduced singly and in progressively increasing doses. After one anti-microbial agent was successfully introduced, the second was started. When the patient could tolerate two or three chemotherapeutic drugs, the dosage of steroid hormone was reduced gradually over a three to five week span. The patient was followed with periodic sputum examinations and chest x-rays to evaluate the effect of therapy on the underlying disease.

Case 1: J. W., 41 year old white woman, was admitted August 25, 1955 (third admission), in an acutely toxic state, with an intractable harsh cough, positive sputum for tubercle bacilli, hoarseness, high fever, anorexia, gastric intolerance to PAS and pruritic erythematous eruption due to dystricin.** Isoniazid was the sole drug she could accept. On admission, her chest x-ray film revealed a giant antrum with fluid level in the right upper lung field and productive infiltration bilaterally. Her clinical course was one of progressive deterioration. An intradermal test, with 1-1000 streptomycin, revealed a positive immediate and delayed reaction. The past history disclosed allergic perennial vasomotor rhinitis.

Steroid therapy, ACTH-gel 80 units daily, which was the initial minimum dose required to suppress reaction, was instituted on September 16, 1955 and concluded on October 24, 1955. Consequently she could tolerate dystricin 1 gram q. day for 10 days, followed by 2 grams weekly, and PAS 12 grams daily. She also received isoniazid

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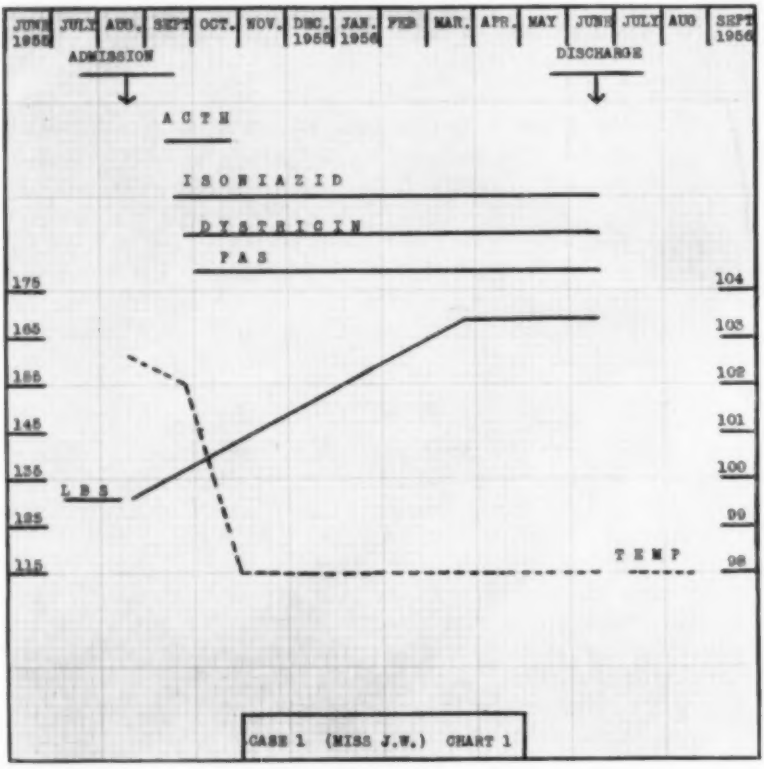
**Dystricin: equal parts streptomycin and dihydrostreptomycin (Squibb).

200 mg. t.i.d. Her clinical condition improved impressively. The skin eruption, cough, hoarseness, anorexia, fever, mental apathy, sputum and pulmonary lesion improved promptly. She gained 40 pounds in six months. Due to symptoms of peripheral neuropathy, pyridoxine 50 mg. t.i.d was added to the regimen. The neuropathy manifestations regressed slowly. Dystricin was discontinued after 18 months' administration,



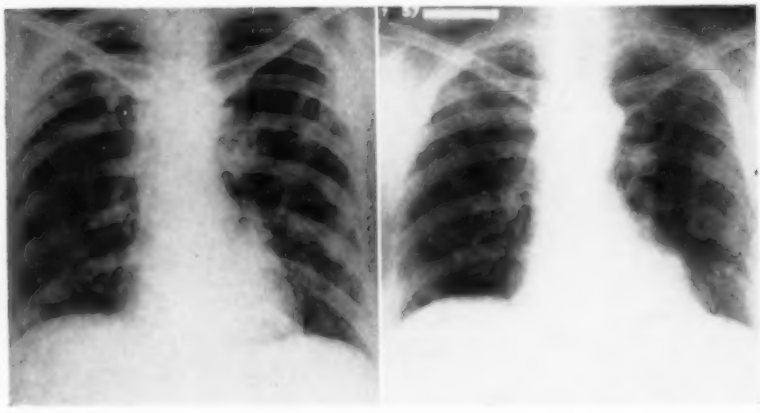
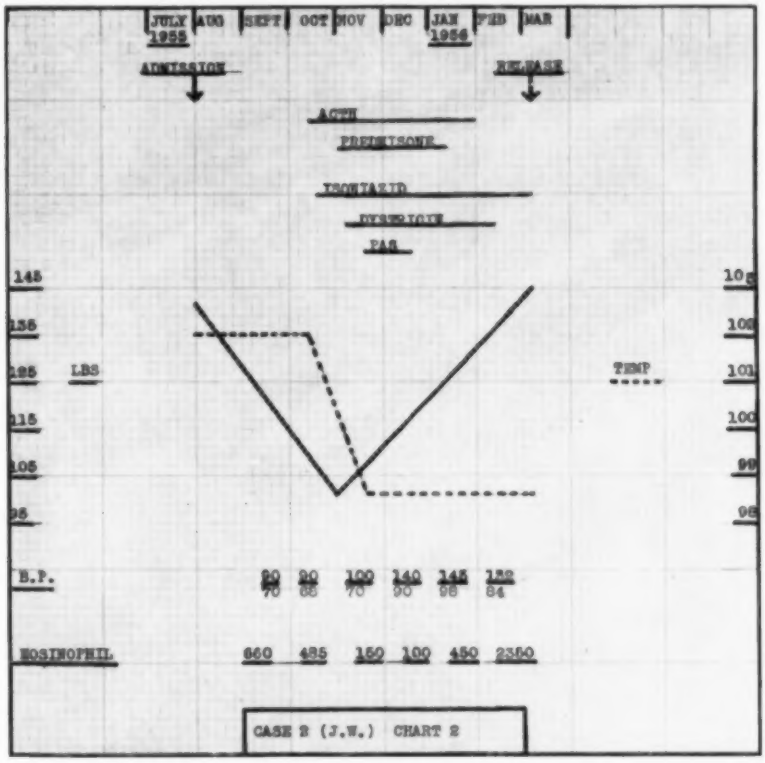


FIGURE 1A FIGURE 1B

Figure 1A, CASE 1: Pre-steroid, August 2, 1955.—*Figure 1B*: Post-steroid, June 7, 1957.

post steroid, due to recurrence of skin reactions. At present she satisfactorily assimilates PAS and isoniazid. The sputum converted from positive to negative on January 1, 1956 and has persisted negative to date, July 3, 1957. The pulmonary lesion which had regressed considerably now remains stable and inactive, without evidence of residual cavitation (Fig. 1 and Chart 1).



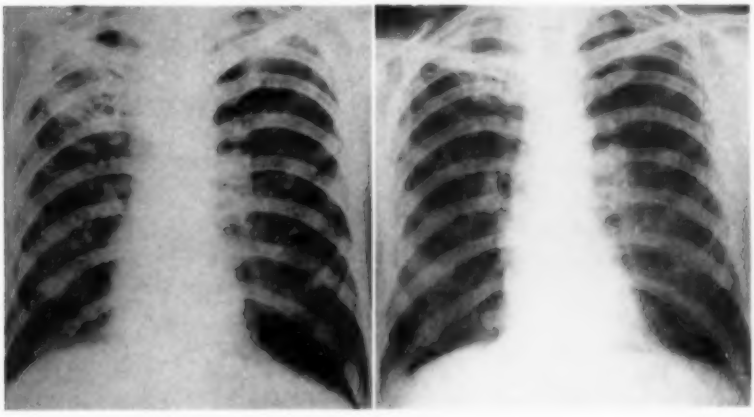
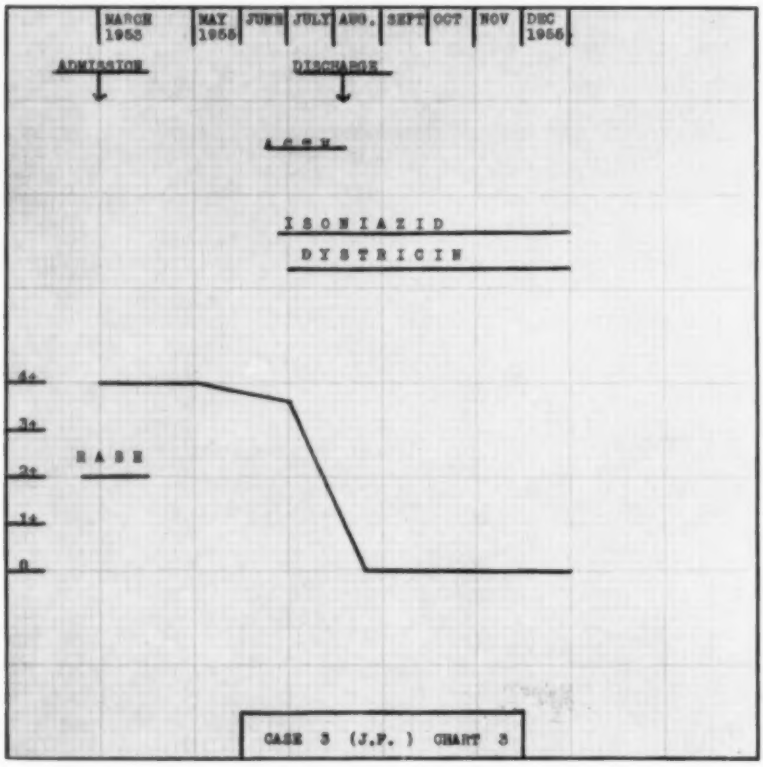


FIGURE 2A FIGURE 2B

Figure 2A, CASE 2: Pre-steroid, October 7, 1955.—*Figure 2B*: Post-steroid, June 13, 1957.

Case 1 Summary: This is an allergic patient with an extremely guarded prognosis due to a highly toxic state, the result of far advanced active pulmonary tuberculosis and untoward drug response to dystricin and PAS. Following the combined use of steroids and anti-tuberculous agents these results became evident: A—Tolerance to



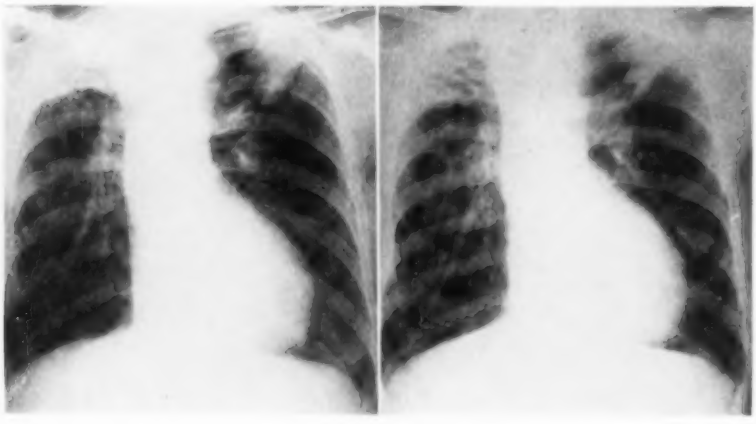
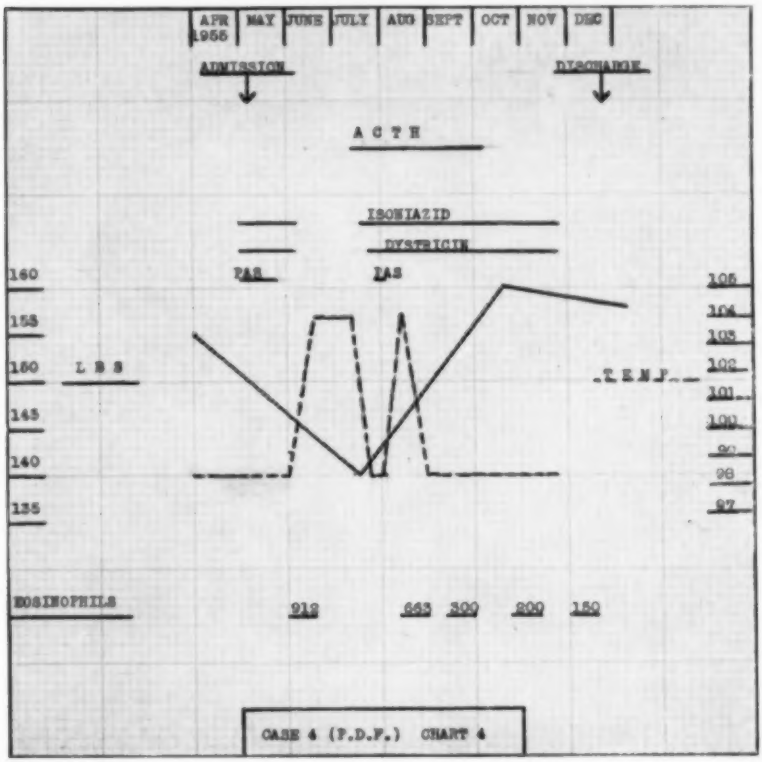


FIGURE 3A FIGURE 3B

Figure 3A, CASE 3: Pre-steroid, March 8, 1955.—*Figure 3B:* Post-steroid, April 30, 1957.

dystricin and PAS promptly improved; B—Quick subsidence of toxic state; C—Regression of the giant antrum and pulmonary infiltrate; D—Prompt reversal of positive to negative sputum; E—No untoward effect of steroid therapy on the tuberculous pulmonary process.

Case 2: J. W., 47 year old white man was admitted on September 14, 1954 with complaint of weight loss, anorexia, cough and expectoration. The sputum was positive



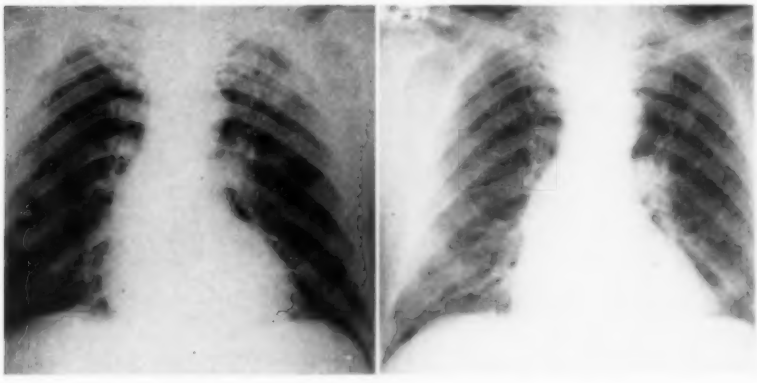
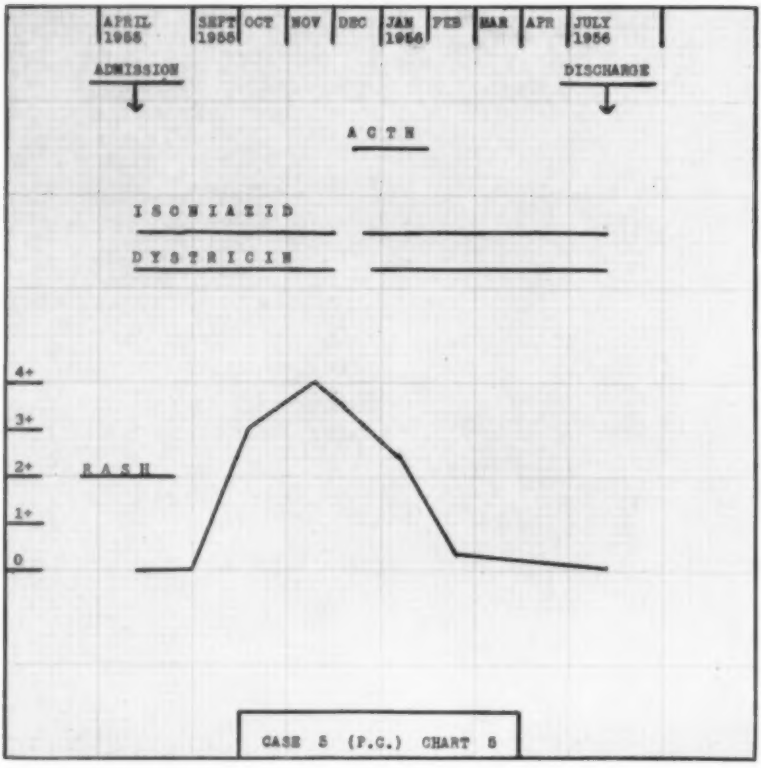


FIGURE 4A FIGURE 4B

Figure 4A, CASE 4: Pre-steroid, April 27, 1955.—*Figure 4B:* Post-steroid, May 28, 1957.



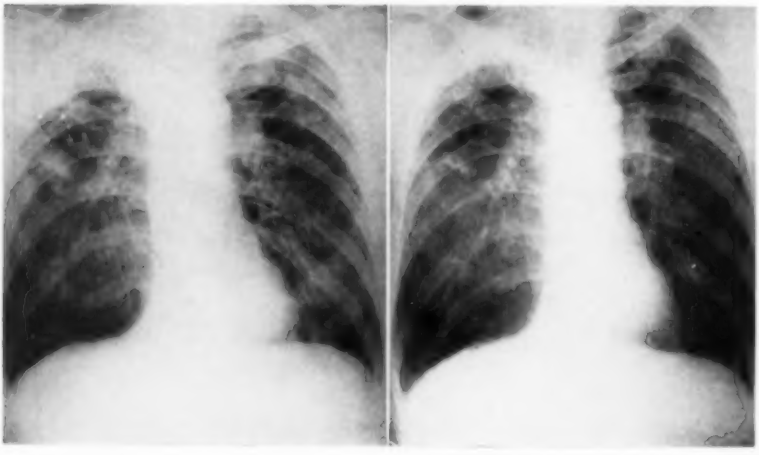


FIGURE 5A FIGURE 5B

Figure 5A, CASE 5: Pre-steroid, October 25, 1955.—*Figure 5B:* Post-steroid, June 21, 1957.

for tubercle bacilli and chest x-ray film showed bilateral exudative, fibro-nodular and cavitary lesion. He was placed on a regimen of dystricin, isoniazid and PAS. In a short time he developed a pruritic eruption, angioedema, fever, anorexia, weight loss and mental apathy. He appeared to have intolerance to many drugs (dystricin, PAS, isoniazid, viomycin, Stokes expectorant, codeine, dromoran, aspirin, pyribenzamine, benadryl and chlor-trimeton.) The most severe reaction occurred 24 hours after an injection of dystricin. He exhibited an acute exfoliative dermatitis that ultimately required six months to subside. As a consequence, exfoliation of the entire skin, scalp hair, finger and toe nails occurred. At this time all chemotherapeusis was suspended for nine months to permit the reaction to abate. In this interval the pulmonary lesion had partially subsided and he regained some weight. On July 12, 1955 he signed a release from the hospital. This untoward reaction to dystricin was interpreted as an accelerated serum sickness type reaction.

J. W. was readmitted August 11, 1955 with complaint of anorexia, dysphagia, weight loss, insomnia, mental depression and the sputum positive for tubercle bacilli. The administration of a teaspoon of Stokes expectorant immediately provoked a pruritic rash, angioedema and fever. After this reaction subsided he ingested a single tablet of isoniazid. This immediately induced fever, angioedema, generalized pruritic eruption and the onset of heavily blood-streaked sputum. His symptoms rapidly became worse, including dysphagia, sore throat, hoarseness, anorexia and thirty-eight pound weight loss in two months.

Steroid therapy was initiated on October 15, 1955 and was terminated on January 25, 1956. His initial minimum dose of steroid hormone required to suppress the reaction consisted of ACTH-gel 120 units q.day and prednisolone 10 mgm, t.i.d. by mouth. In addition benadryl 100 mgm. q.i.d. and 50 mgm. in the same syringe with the dystricin, and prednisolone ointment locally, were necessary supplements to suppress the untoward reaction. He tolerated dystricin for a few months, then he refused it, due to a phobia of a reaction. He tolerated PAS for three weeks, then he discontinued it, due to gastrointestinal symptoms. Isoniazid 100 mgm. t.i.d. was taken with impunity. He has continued to use isoniazid as his sole antituberculous agent.

Shortly after steroid therapy was started, his depressed mood had reverted to a cheerful optimistic attitude. His dysphagia and sore throat promptly disappeared. The cough and sputum diminished. His appetite became ravenous and he gained fifty pounds in four months. The fever subsided by lysis and remained normal. The blood pressure rose from the hypotensive level of 90/70 to 140/70 in a short time. The total eosinophil count dropped from 660 to 100 with suppression of his symptoms. The undesirable side effects of steroid therapy were minimal due to careful attention to the sodium and potassium electrolyte balance. He signed a release from the hospital March 1, 1956, but he continued with isoniazid on an outpatient basis. He was readmitted on April 20, 1956 for the evaluation of an episode of blood streaked sputum that occurred subsequent to strenuous exertion. The clinical course during this admission was satisfactory. He was discharged on July 3, 1956 to the outpatient department for follow-up care. The sputum was converted to negative January 1957 and the pulmonary tuberculosis is arrested 21 months post-steroid therapy (July 1957). (Fig. 2 and Chart 2.)

Case 2 Summary: A case of far advanced active pulmonary tuberculosis with untoward drug reactions to both antimicrobial and symptomatic agents. He had undergone an acute generalized exfoliative dermatitis due to an injection of dystricin, a bout of fever and pruritic rash due to isoniazid, gastrointestinal reaction due to PAS and toxic reaction due to Stokes expectorant. With the combined use of steroid and antituberculous agents the following results occurred: A—Improved tolerance to dystricin. B—Disease toxicity arrested. C—Improved tolerance to symptomatic drugs. D—Conversion of the sputum from positive to negative on culture, twelve months after steroid therapy. E—Regression of the pulmonary lesion with arrest of the disease. F—With the continued use of a single antimicrobial agent, isoniazid, this patient made an excellent clinical recovery to date.

Case 3: J. A. F., a 66 year white man, was admitted to the hospital on March 3, 1953 with the diagnosis of far advanced active pulmonary tuberculosis. He was given dystricin, isoniazid and PAS. Following six weeks of treatment, he noticed a pruritic eruption on his hands and face. This rash would subside when dystricin was withdrawn and recur when it was resumed. These remissions and relapses of pruritic rash typified his clinical course at the hospital. He later developed a lichenified eruption of his face and an extensive crusting, scaling dermatitis on his scalp. He also endured gastrointestinal symptoms to PAS. As the time of his discharge approached, it was urgent to suppress the drug rash, to enable the maintenance of an adequate chemotherapy regimen on an outpatient basis.

Steroid therapy was initiated on June 25, 1955 and was completed on August 4, 1955. Rash suppression was accomplished with ACTH-gel 80 units q. day, as his initial minimum dose, plus pyribenzamine 100 mgm. q.i.d. and hydrocortisone ointment locally, as supplements. As the eruption subsided he gained five pounds. A peptic ulcer diagnosed thirty years ago was not reactivated by the steroid therapy. Sputum cultures for tubercle bacilli have been negative until the present time, July 1957, except for a single positive culture on September 27, 1956. His last chest x-ray, April 30, 1957, shows a

residual bilateral productive inactive process with considerable shrinkage of the right upper lobe and associated post-tuberculous bronchiectasis and emphysema. Twenty-four months post steroid therapy, July 1957, the clinical condition of the patient is good. After 13 months treatment with isoniazid 100 mg. t.i.d. and dystricin 1 gram b.i. weekly, he sustained a reaction thirty minutes after an injection of dystricin. This consisted of amb.yopia for five minutes, generalized aches, malaise and anorexia. Consequently he refused dystricin injections, but has continued with isoniazid as the sole therapeutic agent. (Fig. 3 and Chart 3.)

Case 3 Summary: Case of far advanced pulmonary tuberculosis with a pruritic eruption due to dystricin, gastrointestinal intolerance to PAS and a past history of peptic ulcer which was treated with combined steroid and antimicrobial therapy. The following results were obtained: A—Tolerance to dystricin for thirteen months. B—No reactivation on his peptic ulcer. C—No untoward effect of steroid therapy on the pulmonary lesion. D—Prompt clearing of the drug eruption.

Case 4: P. D. F., a 61 year old white man, was admitted on May 6, 1955 with an infiltration in the left upper lung fie.d. The sputum was negative on culture both on admission and discharge. He was given dystricin and PAS. After several weeks, due to gastrointestinal intolerance, PAS was replaced by isoniazid. On or about June 14, 1955 he had chills and fever succeeded shortly by a severe pruritic maculopapular rash. At this time, all therapy was suspended and an antihistamine was given for symptomatic relief. Nevertheless, the fever persisted and the eruption spread to both ears, both [illegible] areas, both inguinal areas and the anterior aspect of the thorax and the abdomen. The regional lymph nodes draining these respective areas were enlarged and tender. The skin and sclera were icteric. At the height of this reaction, ACTH-gel 80 units q. day was started on July 14, 1955. There was a prompt amelioration of this reaction. Subsequently he swallowed a single 0.5 gram tablet of PAS. This caused an immediate recrudescence of rash, fever and jaundice. This reaction was again controlled by steroid medication. Steroid therapy was terminated on November 5, 1955. He was discharged December 23, 1955 to the outpatient department for follow-up care. Here he was continued on dystricin and isoniazid without untoward effects. At the present time, July 1957, twenty-six months post-steroid therapy, his sputum remains negative on culture and the left upper lung infiltrate which has regressed, continues unchanged and inactive. His clinical condition remains good. (See Fig. 4 and Chart 4.)

Case 4 Summary: Case of pulmonary tuberculosis with an untoward reaction to PAS, manifested by rash, fever and hepatitis. The results accomplished were: A—Prompt disappearance of drug reaction. B—Pulmonary lesion promptly receded. C—No adverse effect on the pulmonary tuberculosis, twenty-six months subsequent to the use of steroids. R—Excellent clinical condition.

Case 5: P. C., A 60 year old white man was admitted for the third time on April 27, 1955 with far advanced pulmonary tuberculosis. On admission, he was placed on dystricin and isoniazid. His clinical condition progressed satisfactorily for six months, including resorption of some of the pu.monary infiltration. During October 1955 he noticed the onset of a pruritic vesicular eruption over both hands. This rash became worse after each injection of dystricin and itched more at night. The lesion advanced to a marked exudative state, associated with numerous traumatic linear excoriations and a profuse seropurulent discharge. Simultaneously a quiescent seborrheic scalp dermatitis became reactivated.

P. C.'s initial minimum dose required to suppress the reaction with ACTH-gel 80 units q. day started on December 18, 1955. This was supplemented with benadryl 100 mg. q.i.d. and hydrocortisone ointment locally, to maintain the ACTH-gel dose at 80 units q. day. The steroid medication was terminated on January 16, 1956 and the dermatitic reaction was also completely ameliorated at this time. He was discharged from the hospital on July 26, 1956 with a negative sputum on culture, which was also negative on admission to the hospital. His pulmonary tuberculosis has remained unchanged as observed on serial x-ray films and fluoroscopic examinations in the year following hospital discharge. His peptic ulcer, noted thirty years ago, has remained quiescent to date. At the present time, July 1957, his clinical condition remains satisfactory. Dystricin was tolerated for eighteen months post-steroid, but was discontinued July 1957 due to recurrence of untoward skin reaction. Isoniazid is tolerated satisfactorily to date. (Fig. 5 and Chart 5.)

Case 5 Summary: Case of far advanced pulmonary tuberculosis with an untoward reaction to dystricin consisting of a pruritic eruption. The results obtained with the therapy outlined above were: A—Tolerance to injections of dystricin for eighteen months. B—Maintenance of negative sputum cultures. C—No exacerbation of the tuberculous disease on x-ray, but on the contrary, regression and stabilization. D—Quiescence of a peptic ulcer diagnosed thirty years ago.

DISCUSSION

The combined use of steroids (supplemented by antihistamines and hydrocortisone ointment locally in three instances) and antimicrobial agents in four cases of far ad-

vanced and one case of moderately advanced pulmonary tuberculosis appears to have produced a prompt salutary effect in extinguishing the drug reaction (pruritic rash, angioedema, fever and hepatitis) and disease toxicity (cough, expectoration, anorexia, fever and malaise) simultaneously. There was regression of tuberculous exudative and recent infiltrative lesions. The mechanism of the steroid anti-inflammatory action is due to its non-specific interruption of the chain reaction of cell destruction triggered by the injurious stimulus of disease toxicity or untoward drug reaction.[1] The anti-inflammatory effects require high unphysiologic concentrations of circulating hormone. This action occurs at the cell level. Any type of inflammatory cell reaction to injury is modified, irrespective of the cause. It prevents the release and enhances the removal of noxious substances from injured cells. Destructive changes in and around the cell are prevented, and up to the state of necrosis, the damage is reversible. It is noteworthy that a giant antrum in Case 1 was not visualized on x-ray films subsequent to the use of steroid. Positive sputum cultures in Cases 1 and 2 were converted to negative cultures. In the remaining three cases, negative sputum cultures at the onset of the above therapy regimen have remained negative. These cases have now been observed from twenty-one to 26 months subsequent to steroid therapy by serial x-ray films of the chest and sputum cultures. No adverse effect on the pulmonary tuberculous disease has been noted to date.

The undesirable effects of high steroid dosage required to suppress the inflammatory response were of minor significance. The steroids were employed in doses sufficient to reduce the total eosinophils by more than fifty per cent. In two cases with peptic ulcer history, there was no evidence that the use of steroid drugs resulted in any reactivation of the ulcer. In Cases 1 and 2 the use of steroids did result in slight sodium and water retention, easily controlled by low sodium diet and the administration of potassium tablets.

It has been reported that the combined use of steroids and antibacterial agents in unusually severe infections has resulted in significant reduction in morbidity and mortality.[2] The combined use of steroids and isoniazid in tuberculous meningitis decreased the morbidity and the mortality from this complication, according to Shane and Riley.[3] However, documented reports of reactivation of latent tuberculous foci, attributable to the prolonged use of steroids in arthritis, deterred their administration in selected cases.[4]

If one may postulate that tuberculous disease toxicity and untoward drug reaction are both manifested through the common channel of inflammatory response, then the steroid hormones which are notably anti-inflammatory, antitoxic and anti-allergic should be beneficial when employed for this coexistent condition.[1, 2, 5] This has been true in five cases cited here. The observation that untoward drug reactions in these cases were manifested by pruritic dermatitis suggests a hypersensitivity mechanism in their formation. A positive skin test for streptomycin was elicited in Case 1. Skin tests were not performed in the remaining cases. In Cases 1 and 5, it is of interest to note that marked reduction in untoward drug reactions to dystricin permitted usage of dystricin for an additional eighteen months. Case 2 had untoward drug reactions to all antimicrobial agents. After steroids he could take isoniazid and dystricin. Untoward drug reaction to dystricin in Case 3 was reduced by steroid to permit its further use for thirteen additional months. Case 4 had an untoward response to PAS that subsided on steroids. But the gravity of the hepatic reaction, while under steroid hormones, in response to an oral retest dose, reminded one of an anaphylactic reaction. In this instance, PAS has been avoided for the safety of the patient.

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SUMMARY

This is a report of five cases of active pulmonary tuberculosis with coexistent untoward drug reactions to one or more antituberculous agents, who were treated by combined steroid and anti-microbial therapy. The impressive results obtained were markedly superior to the previous medical regimen. There was no injurious effect on the underlying tuberculous process, as noted on serial x-ray films of the chest and sputum cultures over a period of twenty-one to twenty-six months following steroid treatment. The steroids are a potent addition to the armamentarium of the clinician in treating tuberculous patients who manifest untoward drug reactions to the chemotherapeutic agents. However, one must be alert to the side effects and physiologic effects of the steroids which may be injurious to the patient.

RESUMEN

Esta es una descripción de cinco casos de tuberculosis pulmonar activa con coexistencia de raecciones a una o más de las drogas antituberculosas. Los resultados obtenidos fueron marcadamente superiores a los del régimen médico previo. No hubo mal efecto

en las lesiones tuberculosas subyacentes según se observó a la radiografía y por los cultivos de esputos por un período de 21 a 26 meses después del tratamiento con esteroides.

Los esteroides son un agregado potente al armamentario del clínico que trata tuberculosos con reacciones colarterales a las drogas. Sin embargo hay que estar pendiente de otros efectos así como de los fisiológicos de los esteroides que pueden dañar a los enfermos.

RESUME

L'auteur rapporte cinq cas de tuberculose pulmonaire active avec des réactions d'intolérance à l'égard d'un ou de plusieurs agents antituberculeux, qui furent traités par la thérapeutique antimicrobienne et la cortisone associée. Les résultats significatifs obtenus furent notablement supérieurs à ceux du programme médical antérieur. Il n'y eut aucun effet toxique sur l'évolution tuberculeuse sous-jacente, comme il fut noté d'aprés une série de clichés radiologiques du thorax et des cultures d'expectoration pendant les 21 à 26 mois qui suivirent le traitement par la cortisone. La cortisone represésenta un complément puissant de l'armement du clinicien dans le traitement des réactions d'intolérance aux agents thérapeutiques. Cependant, on doit être averti des effets secondaires et des effets physiologiques des corticoïdes, qui peuvent être toxiques pour le malade.

ZUSAMMENFASSUNG

Es handelt sich um einen Bericht über 5 Fälle von aktiver Lungentuberkulose mit gleichzeitiger ungünstiger Arzneimittelreaktion auf ein oder mehrere antituberkulöse Stoffe, die mit kombinierter Steroid—und antimikrobieller Therapie behandelt wurden. Die erzielten eindrucksvoller Ergebnisse waren deutlich der früheren internen Behandlung überlegen. Es gab keine schädlichen Wirkungen auf den zugrunde liegenden tuberkulösen Prozess wie sich aus Röntgenbildreihen des Thorax ergab und aus Sputumkulturen während eines Zeitraumes von 21 bis 26 Monate nach der Steroidbehandlung. Die Steroide sind eine wirksame Ergänzung des Rüstzeuges des Klinikers bei der Behandlung von tuberkulösen Patienten, bei denen ungünstige Arzneimittelreaktionen auf die chemotherapeutischen Substanzen in Erscheinung treten. Man muss allerdings auf die Nebenwirkungen und auf die physiologischen Wirkungen der Steroide achten, die für den Kranken schädlich sein können.

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A Study on Intersegmental Septa

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Publications dealing with anatomy of the lung describe only briefly the intersegmental septa, usually referring to them as "intersegmental planes." The existence of such "planes" has been doubted by the authors for years, and an investigation was undertaken by filling cadaver lungs according to the method of Tobin, as follows: 1. In two cases the whole lung was filled with unicolored (white) latex, and 2. In six cases, each segment was filled with a different colored latex. The latex was solidified in 20 per cent formalin.

1. In the *unicolored* specimens the secondary lobuli were marked on the pleural surface equally by connective tissue both in the intersegmental and the interlobular borders. The segments were not bordered by a thicker connective tissue layer than the lobuli; thus in gross appearance the segmental borders were not recognizable.

2. On the smooth pleural surface of the *multicolored* specimens the intersegmental borders were marked only by the different colors and zig-zagged according to the angulated lobuli. (Fig. 1. and 2. A.)

After these observations the authors separated the different colored segments in the intersegmental septa and found that the intersegmental surfaces are not plane, even or smooth, but uneven and bumpy like basalt rocks; the irregular surfaces of the pentagon-shaped lobuli of the neighbouring segments fit into each other as a cast fits to the pattern. (Fig 1. and 2. B.) Naturally not all of the intersegmental surfaces are equally uneven. Less angulated surfaces were seen between the two lingular segments and between some basal segments. (Fig. 2. B.; surface between the lateral and posterior basal segments.)

Utilizing the above observations the authors have created a more life-like segmental model, in which the intersegmental unevenness caused by protrusion of the angulated lobuli was imitated. (Fig. 3.)

The above statements have considerable anatomical significance, but they have also some clinical importance:

1. Surgeons find the intersegmental surfaces fairly smooth and plane-like in segmental resections, but this is, as consequence of above statements, because of the collapse of the lobuli. However, a larger lobulus can protrude occasionally into a neighbouring segment (Fig. 2. B.) and create a larger elevation on the surface in spite of its collapse. *Overholt* and *Langer* write in their book (The Technique of Pulmonary Resection, 1949) that "With extreme rarity small intersegmental bronchi are encountered." One may ask (a) whether this impression may be the result of unintentional division through the interlobular septum or lobular bronchus projecting from the segment being removed into the adjacent one (or vice versa)? and (b) whether such an occurrence might not explain an otherwise unexplained post-operative bronchial fistula?

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2. In cases of segmental atelectasis x-ray films show the interlobar border of the segmental shadow marked and sharp, but the intersegmental ones indistinct, fuzzy or zig-zag. These findings could be attributed to two reasons:

a. The collateral ventilation may permit air to enter the atelectatic segment near the border through the pores between the alveoli of the neighbouring segments and thus make these surfaces indistinct or fuzzy.

b. An atelectatic segment never collapses like an atelectatic lobe. Atelectasis in a segment occurs only if secretion or excretion occludes the pores and thus obstructs the collateral ventilation. The segments in cases of acute atelectasis do not diminish considerably in size. They shrink only by fibrosis.

In these circumstances according to the above statements the aerated lobuli of the neighbouring segments protrude into the atelectatic segment

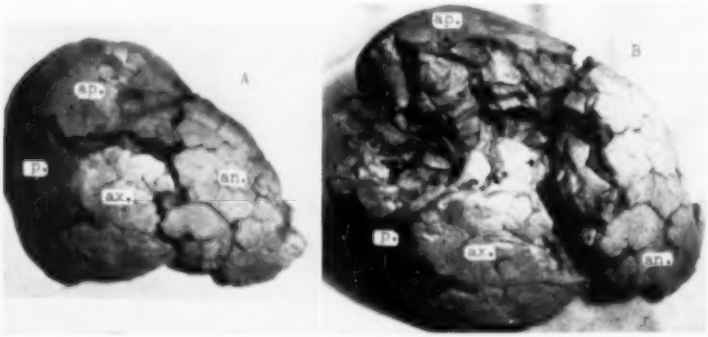

FIGURE 1: Lateral view of a right upper lobe. Each segment is filled with different colored latex and separated in the intersegmental septa. In "A" the segments are in place; in "B" the intersegmental surfaces are seen. Note the lobuli separated by a connective tissue layer and their angulated, zig-zag lines in the intersegmental borders (A), and their angulated protrusion, like basalt rocks, on the intersegmental surfaces (B). "ap." = apical, "p." = posterior, "ax." = axillary and "an." = anterior.

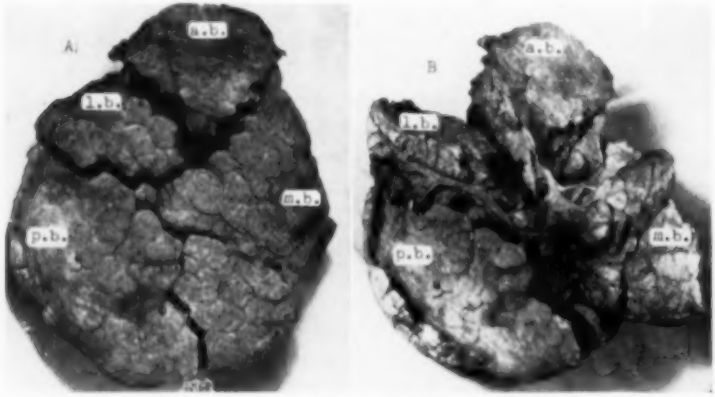

FIGURE 2: Right lower lobe viewed from the diaphragmatic surface. Made as specimen in fig. 1. Note on both "A" and "B" the pronounced elevation of lobuli of the medial basal segment and on "B" the intersegmental veins. "a.b." = anterior basal, "l.b." = lateral basal, "p.b." = posterior basal and "m.b." = medial basal.

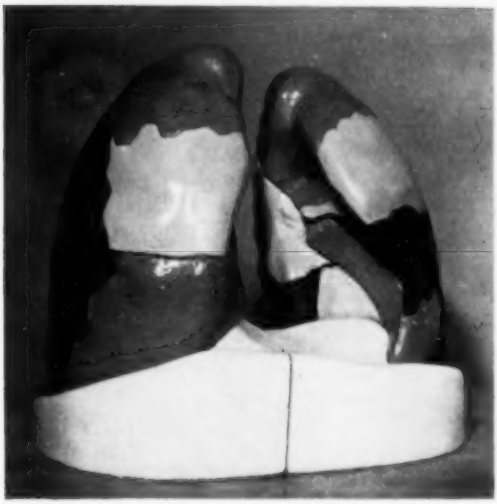

FIGURE 3: Segmental model of the authors.

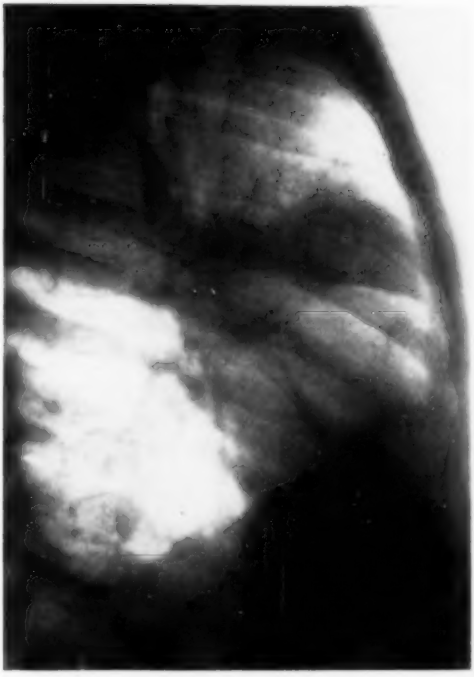

FIGURE 4: Lateral chest x-ray film of a seven year old girl. Note distinct and sharp border of atelectatic shadow of the anterior segment in the interlobar (horizontal) fissure and indistinct border in the intersegmental septum.

and make the shadow of the intersegmental border uneven or zig-zag. The same may be observed also in fibrotic shrunken segments. (Fig. 4.)

SUMMARY

With anatomical, experimental studies the authors found that the intersegmental septa are not plane, as they have been described, but uneven and bumpy like basalt rocks. The irregular surfaces of the pentagon-shaped lobuli of the neighbouring segments were found to protrude and fit into each other as a cast fits to the pattern. Utilizing these observations the authors have created a more lifelike segmental model and have given the explanation for some surgical and x-ray observations.

RESUMEN

Después de estudios anatómicos y experimentales los autores encontraron que las divisiones intersegmentarias no son planas como se han descrito, sino irregulares y accidentadas como las rocas de basalto. Las superficies irregulares de los lobulillos de forma de pentágonos de los segmentos vecinos se encontró que sobresalen y se adaptan unos a otros como acomodándose a un molde.

Usando estas observaciones los autores han creado un modelo de segmentos más ajustado a la realidad viviente y han dado la explicación de algunas observaciones quirúrgicas y radiológicas.

RESUME

Par des études anatomiques et expérimentales, les auteurs ont constaté que les cloisons inter-segmentaires ne sont pas planes, comme on les a décrites, mais rugueuses et pleines de protubérances comme des roches basaltiques. Les surfaces irrégulières des lobules de formes pentagonales constituant les segments contigus sont protubérantes et constituées de façon à s'encastrer les unes dans les autres, comme un moule s'adapte à l'objet qu'il façonne. En utilisant ces observations, les auteurs ont établi un modèle de segment plus conforme à ce qui existe chez le vivant, et ont donné l'explication de quelques observations chirurgicales et radiologiques.

ZUSAMMENFASSUNG

Anhand von anatomischen und experimentellen Studien ermittelten die Autoren, dass die intersegmentalen Septen nicht plan sind, wie sie beschrieben wurden, sondern uneben und holprig, wie Basaltsteine. Es stellte sich heraus, dass die irreguläre Oberfläche der fünfeckig gestalteten Lobulie der benachbarten Segmente überhängen und sich einander einfügen, wie eine Gussform in das Modell passt. Unter Verwendung dieser Beobachtungen haben die Autoren ein mehr naturgetreues Modell eines Segmentes geschaffen und die Erklärung gegeben für einige chirurgische und röntgenologische Beobachtungen.

A Two- to Nine-Year Survey of Chest Surgery for Pulmonary Tuberculosis in British Columbia Indians*

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The 31,000 native Indians in the province of British Columbia, while comprising only 2 per cent of the population, accounted for 28 per cent of the sanatorium admissions and 10 per cent of the patients receiving major chest surgery for tuberculosis, during the years 1948 through 1955.

This study deals with the 166 British Columbia Indians who under the care of Indian Health Services have had major surgery for their pulmonary tuberculosis and been followed from two to nine years for operations completed during this period.

The indications for operation were those generally accepted at the time. It is to be noted that 46 per cent were classed as far advanced disease and that 52 per cent were positive by culture at the time of their surgery. The youngest patient was eight with a pneumonectomy. The oldest resection was 50 and the oldest thoracoplasty 57.

Table I shows the breakdown of patients by definitive procedure and highlights the operation used.

TABLE I

THORACOPLASTY AND VARIATIONS		94
Definitive Thoracoplasty	64	
Thoracoplasty and Apicolysis	19	
Thoracoplasty and Plombage	8	
Plombage	3	
RESECTIONS		72
Pneumonectomy	6	
Lobectomy	47	
Segmental	8	
Wedge	11	
TOTAL		166

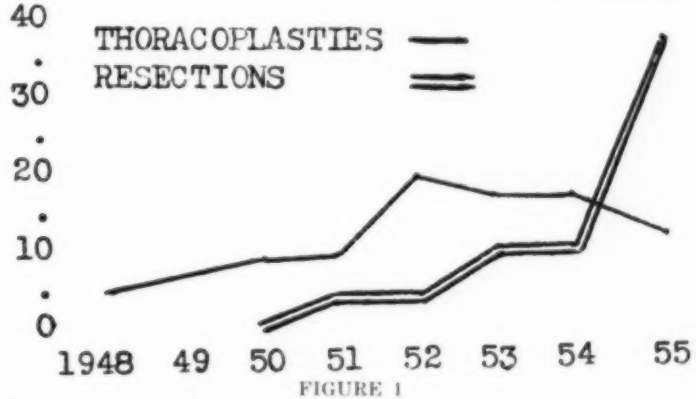

FIGURE 1

*Presented at the Annual Meeting, Pacific Northwest Chapter, American College of Chest Physicians, Portland, Oregon, November 8, 1957.

**Coqualeetza Indian Hospital.

TABLE II

	No.	Per Cent
OPERATIVE RESULTS THORACOPLASTICS		
Arrested and discharged	89	95
Improved	2	2
Post-op deaths	3	3
Total complications	11	12
RESECTIONS		
Arrested and discharged	70	97
Improved	—	—
Post-op deaths	2	3
Total complications	11	15

With the resections, 24 (33 per cent) required an associated tailoring thoracoplasty.

The distribution of the surgery by years as shown by figure one indicates a significant increase in resections during the year 1955, coincident with increased facilities. This marked the end of a backlog of patients and from here onward fewer of the old chronic type cases were seen.

The operative results as noted on Table II illustrate the initial good results, especially with thoracoplasty.

Tables III and IV illustrate the post-operative complications occurring in 22 (13 per cent) of the cases.

TABLE III
THORACOPLASTY COMPLICATIONS

Post-op deaths	3
Major wound infections	2
Empyaema	2
Haemopneumothorax	1
Contralateral spread	1
Retinal artery thrombosis	1
Respiratory cripple	1

TABLE IV—RESECTION COMPLICATIONS

Post-op deaths	2
Bronchopleural-fistula alone	4
Bronchopleural-fistula with empyaema	1
Contralateral spread	1
Interstitial emphysema	1
Serum jaundice	1

In Table V the analysis of post-operative deaths shows that respiratory insufficiency secondary to paradoxical respiration can prove to be serious following Semb's thoracoplasty.

TABLE V—ANALYSIS OF POST-OP DEATHS

Pul. Edema (RUL-2 days)	1
Bronch. pleural fistula with empyaema (4 mos after RUL and died 10 mos)	1
Resp. insufficiency (2 and 20 days following Semb's)	2
Acute dilatation of heart (first post-op day Semb's)	1
TOTAL	5

The patient dying with bronchopleural-fistula and empyaema refused further surgery. There were four late deaths with only one due to tuberculosis.

Following discharge there were 11 patients with relapses as noted in Table VI.

TABLE VI—RELAPSES

	No.	Cases	Per Cent
Thoracoplasties	8	89	9
Resections	3	70	4
TOTAL	11	159	7

The relapses are based on evidence of reactivation in previously stable x-ray shadows or by the obtaining of positive culture for tuberculosis after discharge. Of these patients one died in the hospital, six received further medical care and four have not returned to hospital. Comparison with 10 other published series in this period shows an over all average of 6 per cent of resections having subsequent relapse.[1-10] Two series of thoracoplasties in this period, with antimicrobial drugs show an average relapse rate[11,12] of 7 per cent.

TABLE VII
TWO TO NINE YEAR RESULTS WITH 94 THORACOPLASTIES

	No.	Per Cent
Deaths	5	5
Survivors	89	95
Arrested and Well	84	94
Active or in hosp.	5	6

The results at two to nine years are seen in Tables VII and VIII where it is noted that in the two groups of patients 94 and 96 per cent of the survivors have arrested disease.

The arrested and well and active or in hospital figures refer only to the survivors in these two tables.

TABLE VIII
TWO TO NINE YEAR RESULTS WITH 72 RESECTIONS

	No.	Per Cent
Deaths	4	6
Survivors	68	94
Arrested and Well	65	96
Active or in hosp.	3	4

These results we believe speak for themselves.

All these patients received available antimicrobial drugs during hospital stay but rarely afterward. The average post-operative stay was 16 months for thoracoplasties and 11 months for resections. Twenty three (15 per cent) left against medical advice after staying the same average times.

It has been noted by many surgeons that these Indians exhibit a type of healing characterized by much more scarring and fibrosis than is usually seen. We believe this is evidence of a strong tendency to heal their disease especially when given the opportunity. Many have felt that the assistance of thoracoplasty was all that was required to enable many of these patients to control their disease. From the results of this study that view is probably justified. As well, however, the technical difficulties associated with this marked fibrotic reaction have persuaded many to the lesser operation of thoracoplasty.

There were only three cases (3 per cent) where resection was necessary because of "failed thoracoplasty." This compares favourably with 15 per cent of cases in Paine's series in a "white" sanatorium during the same antibiotic era. Bilateral surgery was carried out in four patients with good results in all; one with thoracoplasties, another with Semb's procedures, a third with lobectomy followed by plombage and a fourth case with two lobectomies.

Of interest to us has been the study of pregnancy in tuberculous patients following chest surgery. Of the 77 women survivors in this series 34 (44 per cent) bore 53 babies. Only one woman, with unstable disease, who left against medical advice following thoracoplasty, had a relapse subsequent to her pregnancy. These figures are similar to those noted in "white" women.[13]

The first 55 cases have a five year follow up. Two non-tuberculous deaths occurred. The remainder are all arrested and apparently well at present, giving 100 per cent of these survivors with a successful result at this time.

CONCLUSION

The conclusion with this study is that we can demonstrate that the British Columbia Indian, while showing a 14 fold morbidity with pulmonary tuberculosis, at the same time shows a marked ability to heal his disease with few breakdowns, comparable at least to that of the "white" population, when given adequate therapy.

SUMMARY

1. Subsequent to major surgery for pulmonary tuberculosis, 166 British Columbia Indians were followed from two to nine years.

2. There were five post-operative and four late deaths in 94 thoracoplasties and 72 resections leaving 95 per cent survivors. Broncho-pleural-fistula occurred in five resections.

3. Nine per cent of the thoracoplasties and four per cent of the resections had relapses after 16 and 11 months of post-operative hospital care respectively. Pregnancy in 44 per cent did not contribute to relapse.

4. Survivors showed 94 per cent of thoracoplasties and 96 per cent of resections to be well with arrested disease.

5. The report reveals that the British Columbia Indian who has a tuberculous morbidity rate 14 times that of the rest of the province when given adequate therapy shows a response equal to the rest of the population in the province.

RESUMEN

1. Después de cirugía mayor por tuberculosis pulmonar, 166 indios de la Colombia Británica se observaron durante 9 años.

2. There were five post-operative and four late deaths in 94 thoracoplasties and y 72 resecciones dejando 95 por ciento supervivientes.
La fístula bronquial se presentó en cinco resecciones.

3. Nueve por ciento de las toracoplastías y cuatro por ciento de las resecciones tuvieron recaída después de 16 y 11 meses de su estancia hospitalaria postoperatoria. El embarazo de 44 por ciento no contribuyó a la recaída.

4. Los sobrevivientes mostraron 94 por ciento de toracoplastías y 96 por ciento de resecciones con buenos reseultados y enfermedad detenida.

5. Esta comunicación demuestra que los indios de la Colombia Británica que tiene una morbilidad tuberculosis 14 veces mayor que la del resto de la provincia, cuando se les somete a tratamiento adecuado muestran una respuesta igual a la del resto de la población de esa provincia.

RESUME

1. 166 Indiens de la Colombie Britannique ont été suivis de 2 à 9 ans après intervention chirurgicale pour tuberculose pulmonaire.

2. Il y eut cinq morts post-opératoires et quatre plus tardives sur 94 thoracoplasties et 72 résections, laissant 95% des malades en vie. Des fistules bronchopleurales furent constatées dans cinq cas de résections.

3. 9% des thoracoplasties et 4% des résections eurent des rechutes après respectivement 16 et 11 mois de soins hospitaliers post-opératoires. La grossesse chez 44% des malades ne contribua pas à la rechute.

4. Les survivants montrèrent que 94% des thoracoplasties et 96% des résections avaient permis l'arrêt de la maladie.

5. Cette communication révèle que l'Indien de la Colombie Britannique dont le taux de morbidité tuberculose est 14 fois plus grand que celui du reste de la province, lorsqu'il reçoit le traitement convenable, répond de la même façon que le reste de la population de la province.

ZUSAMMENFASSUNG

1. Im Anschluss an grössere chirurgische Eingriffe wegen Lungentuberkulose wurden 166 Indianer von British Columbien 2-9 Jahre nachbeobachtet.

2. Es ereigneten sich 5 postoperative und 4 späte Todesfälle unter 94 Thorakoplastiken und 72 Resektionen, so dass 95% überlebten. Bronchopleurale Fisteln traten bei 5 Resektionen auf.

3. 9% der Thorakoplastiken und 4% der Resektionen bekamen Rückfälle nach 16 bzw. 11 Monaten postoperativer Anstaltsbehandlung. Schwangerschaften bei 44% hatten keinen Einfluss auf Rückfälle.

4. Von den Überlebenden erwiesen sich 94% der Thorakoplastiken und 96% der Resektionen als wohlauf und mit zum Stillstand gekommenen Befunden.

5. Dieser Bericht ergibt, dass die Indianer von British Columbien, deren Morbiditäts-Ziffer tuberkulose das 14 fache der übrigen Provinz betrug, unter adäquater Therapie eine Reaktion aufweisen die der übrigen Provinzbevölkerung entspricht.

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Clinical and Roentgenologic Signs of Collagen Diseases Involving the Thorax*

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I. Introduction

In 1941, Klemperer and his colleagues[21] applied the term "collagen disease" to a group of disease of obscure etiology distinguished by a systemic alteration of the connective tissue, especially of its extracellular components, throughout the body. Histologically this group is characterized by the accumulation of fibrinoid,[22] a homogeneous, eosinophilic refractile material which has some of the tinctorial properties of fibrinoid.

Hundreds of articles have appeared in the medical literature concerning the classification, etiology, pathology, clinical features, roentgenologic findings and treatment of the various collagen diseases. An excellent historical and clinical survey is presented in the recent monograph by Talbott and Ferrandis.[37]

Most authors include among the collagen diseases such conditions as polyarteritis (periarteritis nodosa), disseminated or systemic lupus erythematosus, systemic scleroderma and dermatomyositis. Some authors would also include rheumatic fever, rheumatic pneumonitis and rheumatoid arthritis.[11, 14] Other diseases sometimes included in this group are Schonlein's purpura, thrombotic thrombocytopenic purpura, erythema nodosum, some cases of glomerulonephritis, serum sickness, transfusion reactions, thromboangiitis obliterans and ulcerative colitis.[33, 37]

The clinical and pathologic features of the various collagen diseases are not always distinct, and there may be overlapping or transitional types of syndromes. The symptoms of signs of rheumatoid arthritis sometimes appear as part of the total clinical picture of disseminated lupus erythematosus and other collagen diseases, and signs of both disseminated lupus erythematosus and polyarteritis may be seen at autopsy. In well developed cases scleroderma and dermatomyositis are often difficult to distinguish.

Another controversial condition sometimes considered as a collagen disease is Wegener's granulomatosus.[38] This is a syndrome characterized by sinusitis necrotizing granuloma of the upper and lower portions of the respiratory tract, renal insufficiency, arthralgia and diffuse vasculitis, with a circumscribed and occasionally cavitating pulmonary parenchymal lesion which may resemble metastatic disease. This may be a renal respiratory subtype of polyarteritis.

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This material is an abridgement of part of a thesis submitted by Dr. Menon, on leave from the Stanley Medical College, Madras, India, to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Radiology.

TABLE I
INCIDENCE AND MEANS OF DIAGNOSIS

	Autopsy	Biopsy	Clinical	Total
Polyarteritis Nodosa	17	9	14	40
Disseminated Lupus Erythematosus	8	21	8	37
Scleroderma	4	8	8	20
Dermatomyositis	2	3	2	7
Rheumatic Pneumonitis	3	0	2	5
	34	41	34	109

The purpose of this paper is to summarize the clinical, pathologic and especially the roentgenologic data from 109 patients with five collagen diseases admitted to the University of Minnesota Hospitals from 1942 to 1956. Chief emphasis is given to those conditions which involve the thoracic structures and these include polyarteritis, disseminated lupus erythematosus, systemic scleroderma, dermatomyositis and rheumatic pneumonitis. In over two-thirds of these patients the diagnosis was verified by autopsy or biopsy and in the remainder there were strong clinical and laboratory data to substantiate the diagnosis. The incidence and means of diagnosis of the five collagen diseases included in this series are given in Table I.

II. Etiology

The etiology of all of the collagen diseases remains obscure. Experimental[3, 7, 10, 31, 33] and clinical[32] data have been cited to support the importance of a state of hypersensitivity as the development of collagen diseases, especially polyarteritis and disseminated lupus erythematosus, but apparently this factor is not as striking in some of the others. A sensitive state following streptococcal infections may play a role in rheumatic fever.

In our series of 40 patients with polyarteritis nodosa, 19 gave a history that might lead to hypersensitivity. These include injection of penicillin,

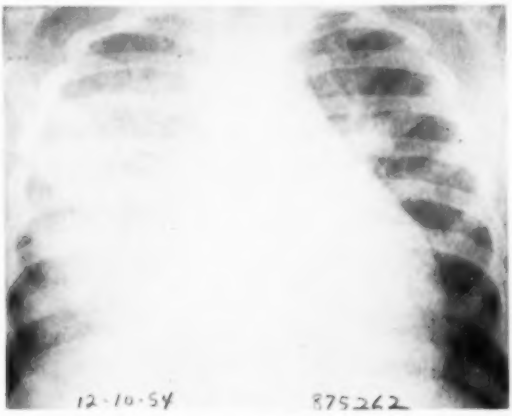

FIGURE 1: Polyarteritis nodosa. Cardiac enlargement, prominent hilar shadows and perihilar edema demonstrated after onset of severe renal failure.

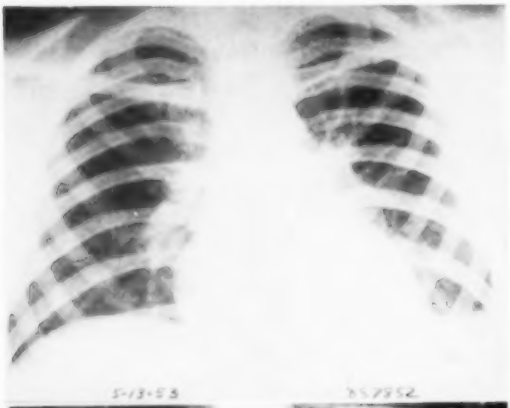

FIGURE 2A

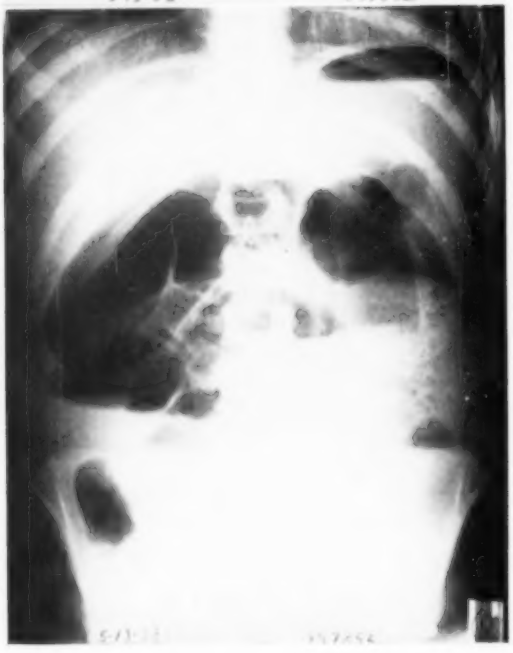

Figure 2: Polyarteritis nodosa. A. Left basal pneumonitis and pleural effusion, hilar shadows prominent, moderate cardiac dilatation without peripheral pulmonary vascular engorgement. B. Partial small bowel obstruction. C. Section of myocardium. Arterial thickening and inflammation, narrowing of arterial lumen, fibrinoid degeneration in wall of vessel. D. Section of Lung. Healed periarteritis.

FIGURE 2B

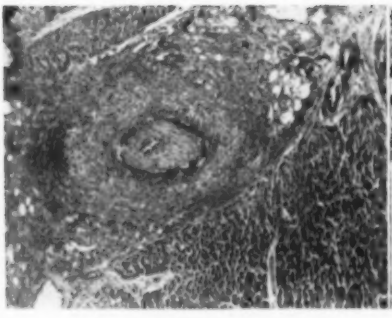

FIGURE 2C

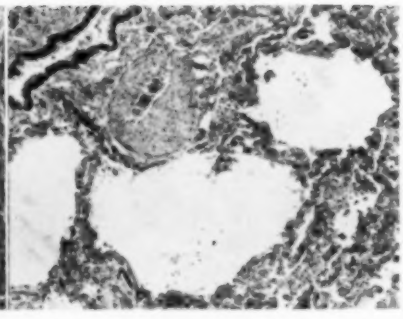

FIGURE 2D

streptomycin, blood transfusions, vaccines, estrogens or a history of bronchial asthma and urticaria. Among 37 patients with disseminated lupus erythematosus one had multiple food allergies, two had received sulfonamides, seven had an eosinophilia and many complained of photosensitivity. Two of five with rheumatic pneumonitis showed a three-plus C-reactive protein test. These data support the role of hypersensitivity in these conditions.

III. Clinical and Laboratory Manifestations

Since all five of the diseases under consideration involve multiple symptoms, including the skin, respiratory system, cardiovascular, urinary and gastrointestinal systems, it is not surprising that the onset in each condition may be variable and that clinical and laboratory findings may be similar or overlap in some patients.[13]

Polyarteritis nodosa has perhaps the most bizarre clinical picture[23] due to widespread vascular involvement which eventually comprises the circulation to various organs. In different patients a history of hypersensitivity to serum or drugs, recently acquired bronchial asthma or cutaneous eruptions or convalescence from an infectious process or acute rheumatic fever appears to initiate the process. A triad of myositis, abdominal pain and weight loss has been described.[14] Hypertension appears sometime during the disease in 40 per cent of the patients and is thought to occur during the healing phase of renal vascular lesions.[8]

An unusual urinary sediment which contains red cell casts indicating acute renal involvement and waxy or hyaline casts indicating chronic renal involvement has been described in polyarteritis and disseminated lupus erythematosus. This has been termed "telescopic" urinary sediment. Albuminuria and urinary sediment indicating changes similar to chronic glomerulonephritis may be seen in all of the systemic collagen diseases.

Leukocytosis is common in polyarteritis, as well as in the other collagen conditions, with the exception of disseminated lupus erythematosus, in which leukopenia is more common. Eosinophilia is most common in polyarteritis but is seen to a moderate degree in some patients with disseminated lupus erythematosus.

Secondary anema, reversal of albumin-globulin levels in plasma, elevated erythrocyte sedimentation rate and various electrocardiographic abnormalities are common in all of these conditions.

In disseminated lupus erythematosus the cutaneous eruption is most common and most characteristic, namely the "butterfly" rash over the nose and face. In this condition sexual predominance is also most apparent, the condition definitely being more common in young women. This condition also has one of the most specific laboratory tests, namely the LE cell or LE rosette phenomenon.[18]

In scleroderma the peculiar hardening of the skin and subcutaneous tissues is one of the most prominent clinical features. Clinical types include: 1) diffuse scleroderma; 2) acrosclerosis, a combination of Raynaud's phenomenon and scleroderma; and 3) circumscribed scleroderma or morphea. Raynaud's phenomenon is present in over half of the patients, and dysphagia in roughly one third.[20]

Dermatomyositis produces a hardening of the skin and striated muscle.

Respiratory and cardiovascular symptoms are present in most patients and dysphagia in a few. Subcutaneous calcification may be a prominent feature, but may also occur in systemic scleroderma. In advanced stages with extensive calcification it may be almost impossible to differentiate these two conditions.

In rheumatic pneumonitis respiratory distress, cough, chest pain, cyanosis and hemoptysis are prominent and out of proportion to the general health status of the patient and to the degree of cardiac involvement. Evidence of active rheumatic carditis is noted in all cases.[26, 29]

For a summary of the symptoms at onset, laboratory data and electrocardiographic findings of the patients in this series, see Tables II, III, and IV respectively.

IV. Pathology

The formation of fibrinoid in the extracellular space of connective tissue and the widespread involvement of blood vessels form the basis upon

TABLE II
SYMPTOMS AT ONSET IN COLLAGEN DISEASES

	No.	Per Cent
Polyarteritis Nodosa (40 Patients)		
Arthralgia	18	45.0
Respiratory symptoms	11	27.5
Abdominal pain	8	20.0
Cardiovascular	7	17.5
Genitourinary	4	10.0
Disseminated Lupus Erythematosus (37 Patients)		
Skin lesions	35	94.6
Muscle and joint	21	56.8
Loss of weight	18	48.6
Respiratory	11	29.7
Cardiovascular	11	29.7
Allergy	8	21.6
Genitourinary	6	16.2
Scleroderma (20 Patients)		
Skin lesions	18	90.0
Raynaud's phenomenon	13	65.0
Dysphagia	7	35.0
Respiratory symptoms	7	35.0
Cardiovascular	6	30.0
Abdominal	3	15.0
Sjogren's syndrome	1	5.0
Dermatomyositis (7 Patients)		
Respiratory symptoms	6	85.7
Cardiovascular	5	71.4
Skin and muscle (weakness)	4	57.2
Dysphagia	2	28.6
Rheumatic Pneumonitis (5 Patients)		
Respiratory symptoms	5	100.0
Cardiovascular	5	100.0
Fever	5	100.0
Skeletal joints	4	80.0
Tonsillites	2	40.0
Gastrointestinal	1	20.0

which pathologic changes are produced in the various collagen diseases. The pathologic changes vary in the different collagen disorders in that different vessels or organs may be involved more frequently, and the cellular reaction may vary.

Polyarteritis involves chiefly the small arteries and the larger arterioles.[36] The smaller arterioles are involved in producing rheumatoid arthritis and the smallest vessels are involved in disseminated lupus erythematosus, as shown by the tendency to produce the wire-looping effect in the renal glomeruli and the endency to involve serous surfaces.[1, 2] The skin is

TABLE III
LABORATORY DATA IN COLLAGEN DISEASES

	No.	Per Cent
Polyarteritis Nodosa (40 Patients)		
Reversal of A-G ratio (21 cases)	16	76.2
Secondary anemia	25	62.5
Abnormal electrocardiogram	25	62.5
Leukocytosis	26	65.0
Urinary findings of glomerulonephritis	24	60.0
Elevated erythrocyte sedimentation rate	24	60.0
Eosinophilia	16	40.0
Telescopic urinary sediment	13	32.5
Disseminated Lupus Erythematosus (37 Patients)		
Reversal of A-G ratio	27	75.6
Leukopenia	31	83.7
Urine (like glomerulonephritis)	27	75.6
Telescopic urinary sediment	17	45.9
Elevated ESR	26	70.0
Positive LE cell test	24	64.9
Secondary anemia	19	52.4
Abnormal electrocardiogram	15	40.5
Eosinophilia (moderate)	7	18.9
Scleroderma (20 Patients)		
Reversal of A-G ratio	14	70.0
Albuminuria	11	55.0
Elevated ESR	10	50.0
Abnormal electrocardiogram	10	50.0
Secondary anemia	5	25.0
Dermatomyositis (7 Patients)		
Elevated ESR	7	100.0
Secondary anemia	5	71.4
Abnormal electrocardiogram	5	71.4
Albuminuria	4	57.1
Leukocytosis	4	57.1
Reversal of A-G ratio	4	57.1
Rheumatic Pneumonitis (5 Patients)		
Abnormal electrocardiogram	5	100.0
Leukocytosis	5	100.0
Albuminuria	4	80.0
Secondary anemia	4	80.0
Elevated ESR	4	80.0
Reversal of A-G ratio	1*	20.0

*Done in one patient only.

attacked primarily in scleroderma and dermatomyositis. Rheumatic fever attacks the heart most consistently.

Cellular reaction is prominent in the vascular lesions of polyarteritis, consisting chiefly of neutrophils and eosinophils. Cellular reaction is often lacking in disseminated lupus erythematosus. Rheumatoid nodules contain cells which are predominantly mononuclear. The presence of the Aschoff body in the myocardium is characteristic of rheumatic fever. A nonsuppurative inflammatory reaction in the skin, subcutaneous tissues and skeletal muscles is present in dermatomyositis.[5] In scleroderma, there is at first edema and mononuclear cellular infiltration in the subcutaneous tissue, later followed by an abnormal change in the collagen.[15]

The lungs, heart and kidneys are commonly involved in all of the collagen diseases.[15, 16, 39] All organs may be involved to some extent by these disorders.[14] The changes may vary from nonspecific to relatively specific in nature. For example, there may be a non-specific interstitial fibrosis, pneumonitis or pulmonary edema or there may be microscopic changes in the vessels indicating the direct effect of the collagen disorder.

TABLE IV
ELECTROCARDIOGRAPHIC CHANGES IN COLLAGEN DISEASES

Incidence	No. of Patients	No. of Ecg's.	No. Abnormal
Polyarteritis Nodosa	40	35	25
Disseminated Lupus Erythematosus	37	28	22
Scleroderma	20	15	13
Dermatomyositis	7	7	5
Rheumatic Pneumonitis	5	5	5

Type of Change	
Polyarteritis Nodosa	
Left axis deviation	10
Sinus tachycardia	4
Right axis deviation	3
Myocardial infarct of damage	3
Consistent with pericarditis	2
Auricular fibrillation	1
Prolonged S-T segment	1
Right bundle branch block	1
Disseminated Lupus Erythematosus	
Sinus tachycardia	9
Low voltage all leads	5
Left axis deviation	3
Right axis deviation	3
Myocardial ischemia	2
Scleroderma	
Left axis deviation	6
Right axis deviation	2
Right bundle branch block	2
Supraventricular tachycardia	1
IV conduction defect	1
Pericardial effusion	1
Dermatomyositis	
Right axis deviation	1
Sinus tachycardia	1
Low amplitude	1
Myocardial damage	1
Depressed S-T in lead I	1
Rheumatic Pneumonitis	
Prolonged P-R	2
Sinus tachycardia	1
LV preponderance	1
RV strain	1

Likewise, in the heart there may be nonspecific inflammatory or fibrotic changes or there may be direct microscopic evidence of involvement of vessels or of the presence of the characteristic Aschoff nodule of rheumatic fever. In the kidney there may be changes similar to glomerulonephritis, or there may be evidence of a specific type of vascular involvement.

Periarterial fibrosis in the spleen occurs in about half of the autopsies in disseminated lupus erythematosus. This finding is not prominent in the other collagen disorders.

The existence of rheumatic pneumonitis as a separate entity is controversial but the demonstration of thickening of the alveolar septa with fibrinoid in patients with rheumatic fever who develop pneumonitis seems to indicate that this is a pathologic entity.

Of special interest to this study is the fact that 70 per cent of the 17 autopsies performed in patients with polyarteritis had pulmonary changes, and some type of pulmonary change was demonstrated in all of the autopsies in eight patients with disseminated lupus, four with scleroderma, two with dermatomyositis and three with rheumatic pneumonitis. All of these patients had roentgen changes in the chest sometime during the course of the disease, and about two-thirds of all the patients in the series had roentgen findings at some time.

V. Therapy in Collagen Diseases

No therapeutic agent has been found to be consistently effective in collagen disease. However, some beneficial effect is obtained from the

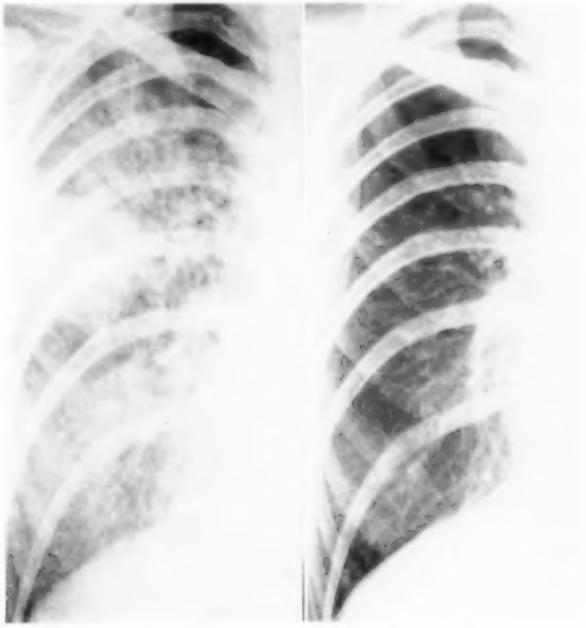

FIGURE 3A FIGURE 3B

Figure 3: Polyarteritis nodosa. A. Interstitial pneumonitis. B. Pneumonitis has resolved following intravenous ACTH.

TABLE V
RESPONSE OF COLLAGEN DISEASES TO STEROID THERAPY

	Total No. in Series	No. Treated with Steroids	Response			
			Very Good	Good	Improved	Poor
Polyarteritis Nodosa	40	18	1	5	6	6
Disseminated Lupus Erythematosus	37	20	0	4	9	7
Scleroderma	20	5	0	0	5	0
Dermatomyositis	7	5	1	0	1	3
Rheumatic Pneumonitis	5	2	0	0	0	2
TOTALS	109	50	2	9	21	18

use of certain drugs and hormones which have anti-inflammatory properties.

In recent years considerable attention has been given to the use of steroids such as ACTH, cortisone and prednisone. At times a patient will receive some benefit from the use of one of the steroids after another has proved ineffective. Unfortunately sufficient doses cannot be administered for sufficiently long periods of time because of side effects such as mental confusion, paranoia, depression, production of peptic ulcer and Cushing's syndrome.

In this series of 109 patients, 50 were treated with steroids. The results in the various diseases are tabulated in Table V.

VI. Roentgen Findings in Collagen Disease

Significant pathologic lesions were found in the lungs, pleura or heart in 28 out of 34 autopsies performed in this series. Since roentgen signs were demonstrated in these structures in approximately two-thirds of the entire series of 109 patients, including those still living, it seems

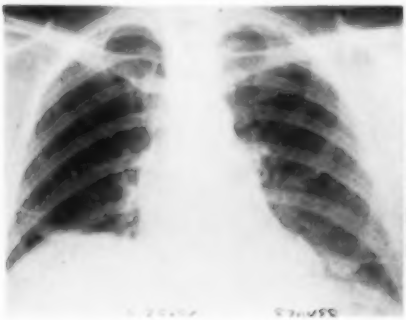

FIGURE 4

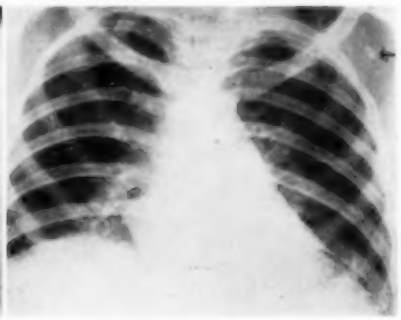

FIGURE 5

Figure 4: Disseminated lupus erythematosus. Cardiac enlargement. Bilateral basal pneumonitis and atelectasis (atelectasing pneumonitis).—*Figure 5:* Disseminated lupus erythematosus. Bilateral interstitial pneumonitis, enlarged heart and pleuropericardial adhesion on right. Calcified left axillary node (arrow).

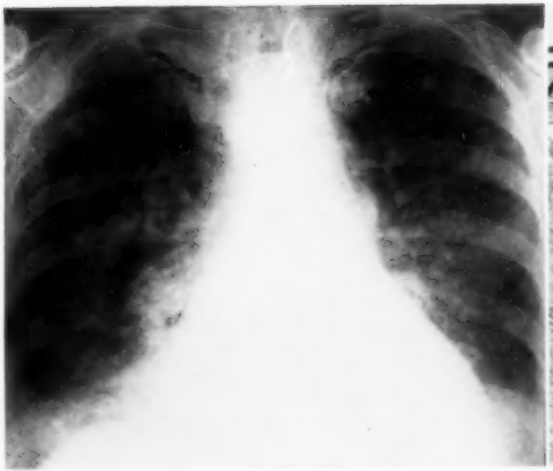

FIGURE 6A

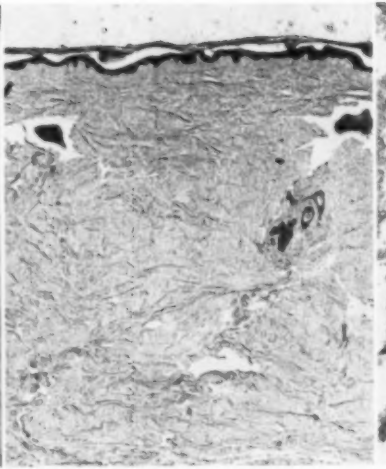

FIGURE 6B

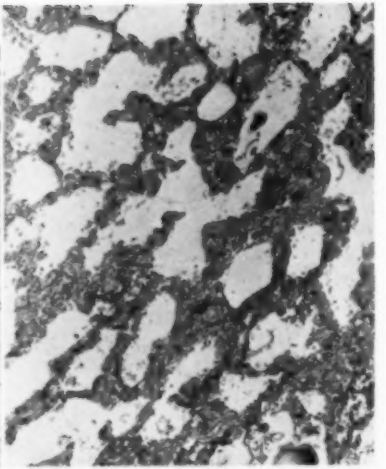

FIGURE 6C

Figure 6: Scleroderma. A. Cardiac enlargement, interstitial fibrosis in lower thirds of both lungs, emphysema, bilateral basal pneumonitis and pleural effusion. Note nodular appearance. B. Section of skin: atrophy of epidermis and appendages; compact collagen masses in the dermis. C. Section of lung: thickening of alveolar septa, fibrosis, and thickening walls of blood vessels.

reasonable to suppose that roentgen signs should appear in the chest at some phase of the disease in over 80 per cent of the patients.

Interstitial pneumonitis, pleural effusion and a nonspecific type of cardiac enlargement occur with sufficient frequency in all five diseases that these signs may be considered as confirmatory in nature and are not usually of great aid in the differential diagnosis of these conditions. Atelectasis is also common, but was not found in our patients with scleroderma.

Several roentgen signs may occur which are rather nonspecific when considered alone, but which assume increased importance when occurring in combination with other signs or when a collagen disease is suspected clinically. For example, bilateral hilar vascular prominence occurs in several clinical conditions, but in the collagen group it is most commonly seen in polyarteritis.[12] Interstitial pulmonary fibrosis and emphysema are also seen in many clinical conditions,[25] but in the collagen group they occur most commonly in scleroderma[28] and dermatomyositis. A honeycomb appearance or peculiar multiple small cyst-like shadows in the lower two-thirds of the lungs[6, 9, 15, 30] is rather characteristic of scleroderma when the sign is present (20 per cent).

Cardiac valvular lesions, pericarditis and pleural effusion are more common in disseminated lupus[19, 27] and rheumatic pneumonitis.[26, 29] Small pulmonary parenchymal nodules are more common in polyarteritis and scleroderma. Small areas of pulmonary consolidation suggesting infarcts may appear in polyarteritis.[35]

Two patients with polyarteritis suffered a unilateral spontaneous pneumothorax and one with dermatomyositis developed bronchiectasis.

Significant roentgen signs are seen less frequently in other organs. Dilatation and lack of peristalsis in the esophagus,[17] absorption of terminal phalanges,[21] calcification of soft tissues and absorption of the periodontal membrane[31] are all seen in some patients with scleroderma. Extensive calcification of subcutaneous tissues is also seen in dermatomyositis, and

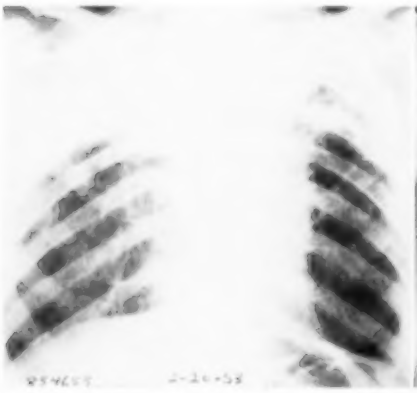

FIGURE 7

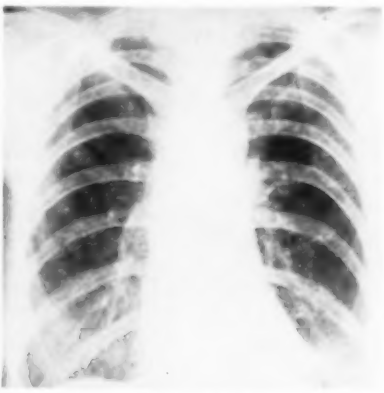

FIGURE 8

Figure 7: Scleroderma. Interstitial fibrosis and peculiar ring-like shadows in both upper lobes (changes more commonly seen in middle and lower lung fields in scleroderma). Basal emphysema, pleural thickening at left base.—*Figure 8:* Dermatomyositis. Bilateral interstitial fibrosis and emphysema.

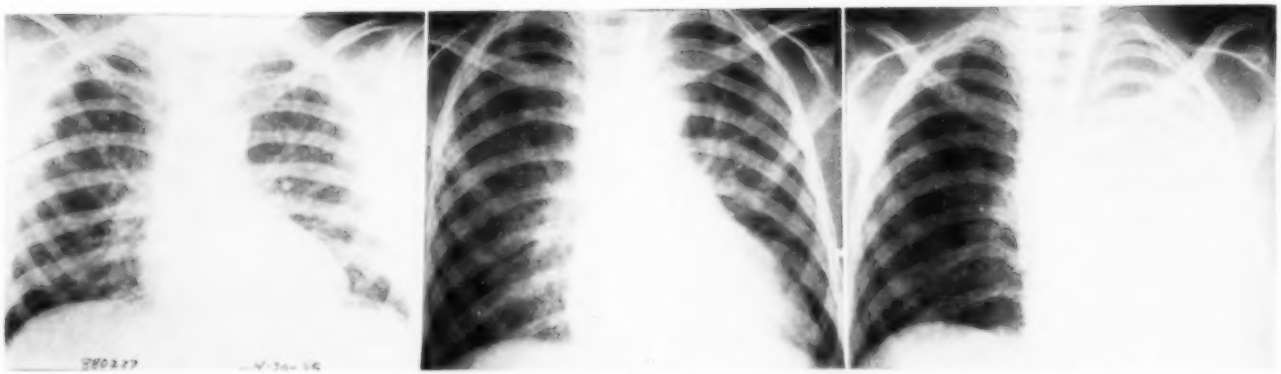

FIGURE 9A FIGURE 9B FIGURE 9C

Figure 9: Dermatomyositis. A. April 30, 1955: Slight cardiac enlargement, minimal bilateral interstitial changes. B. January 14, 1956: Heart larger, increased bilateral interstitial pneumonitis. C. January 27, 1956: Massive atelectasis left lung, interstitial and bronchopneumonia right lung. (Courtesy of *Am. J. Roent., Rad. Ther. and Nuc. Med.*).

grams or barium studies of the small and large intestine occur in polyarteritis and scleroderma. A moderate adynamic ileus was the only significant roentgen sign seen in two patients of this series who developed polyarteritis distal to the resected segment of aortic coarctation.

Roentgen signs of rheumatoid arthritis were seen in three patients with polyarteritis, three with scleroderma and two with dermatomyositis, suggesting that rheumatoid arthritis is part of the systemic disease in these patients. In patients who have rheumatoid arthritis, but who have no renal or other signs of a generalized disturbance, a rather nonspecific interstitial pulmonary fibrosis may occur. This is usually seen when the disease is well advanced and may well be due to restricted thoracic movement with secondary infection due to faulty elimination of infected material from the tracheobronchial tree. If fibrinoid could be demonstrated in the small pulmonary vessels or alveolar walls in these patients it might then be assumed that one of the systemic collagen disorders is developing.

In this series it was noted that many roentgen signs regressed following clinical improvement with steroid therapy. This regression can be quite

TABLE VI
INCIDENCE OF ROENTGEN FINDINGS IN COLLAGEN DISEASES

	Polyarteritis Nodosa	Disseminated Lupus Erythematosus	Scleroderma	Dermatomyositis	Rheumatic Pneumonitis
No. of Patients	40	37	20	7	5
A. Pulmonary Changes					
Hilar enlargement	14	0	0	0	
Pneumonitis	13	17	9	5	5
Pulmonary edema	8	0	0	1	3
Nodular lesions	5	0	3	0	
Pleural effusion	5	12	8	2	1
Atelectasis	4	9	0	1	1
Pulmonary fibrosis	0	3	7	3	0
Emphysema	0	5	7	0	0
Honeycomb or cystic appearance	0	0	4	0	0
Pneumothorax	2	0	0	0	0
Infarction	1	0	0	0	0
Bronchiectasis	0	0	0	1	0
B. Other Changes					
Cardiac enlargement	14	7	9	3	5
Pericarditis	1	6	0	0	3
Ileus	5	1	2	0	0
Rheumatoid arthritis	3	0	3	2	0
Aperistaltic esophagus	0	0	4	0	0
Calcification in soft tissues	0	0	2	1	0
Absorption of phalanges	0	0	1	0	0

in advanced cases with such calcification the differentiation of scleroderma and dermatomyositis may be quite difficult.

Partial obstruction or adynamic ileus demonstrated on plain roentgenostriking in patients with polyarteritis and disseminated lupus erythematosus.

The incidence of the various roentgen signs occurring in this series is given in Table VI. When considered separately each of the signs appears relatively nonspecific or of confirmatory value. However, various combinations of signs or sequential changes may suggest the presence of a collagen disease at some time in roughly one-third of the patients.

VII. Illustrated Roentgen Findings

Selected case histories were taken from this series to show how roentgen signs may be of confirmatory value in the diagnosis or in following the course of a given disease and how various combinations of signs or sequential changes in the roentgenograms may be of differential diagnostic value.

A. Polyarteritis nodosa.

Case 1: A nine year old boy admitted with clinical and laboratory signs of polyarteritis had normal roentgenograms of the chest until severe renal damage precipitated the appearance of cardiac enlargement, prominent hilar vessels and perihilar edema (Fig. 1). Although typical polyarteritis was demonstrated in the small arteries of the lungs at autopsy, the roentgenographic changes appeared only after severe renal damage had occurred.

Case 2: An 11 year old boy was admitted with complaints of intermittent cramping abdominal pain, lethargy and fever. Plain films of the abdomen revealed partial small intestinal obstruction with a mass density in the right lower quadrant. At laparotomy enlarged lymph nodes and constricting adhesions were found in the ileocecal region. The adhesions were released and a 20 cm. segment of small intestine was resected.

Leukocytosis, urinary albumin and casts, and right axis deviation on the electrocardiogram were observed. Roentgenograms of the chest revealed a non-specific cardiac enlargement, bilateral hilar vascular prominence without peripheral pulmonary vascular engorgement, pneumonitis and pleural effusion (Fig. 2A and B). This combination of cardiac, hilar and pulmonary changes without evidence of failure is strongly suggestive of polyarteritis. The roentgenographic demonstration of partial small bowel obstruction adds to this picture.

Case 3: A 29 year old woman was admitted complaining of chronic fatigue, loss of weight, mild acneiform rash, upper respiratory infection, sinusitis, and pain and

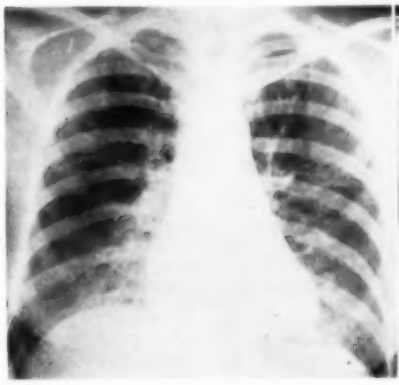

FIGURE 10

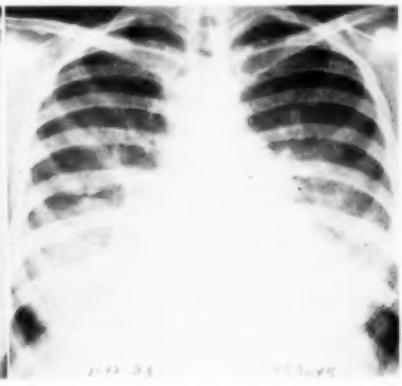

FIGURE 11

Figure 10: Dermatomyositis. Bilateral interstitial pneumonitis. Heart normal or slightly enlarged. (Courtesy of *Am. J. Roent., Rad. Ther. and Nuc. Med.*).—*Figure 11:* Rheumatic pneumonitis. Generalized dilatation of heart, bilateral pneumonitis and pleural effusion, without evidence of cardiac failure.

swelling in the knees and ankles. Elevated erythrocyte sedimentation rate (110 mm. per hour), leukocytosis, reversal of albumin-globulin levels in plasma, sinus tachycardia on ECG, and a trace of albumin and occasional casts in the urine were demonstrated. Roentgenograms of the chest revealed bilateral interstitial pneumonitis which regressed under intravenous administration of ACTH (Fig. 3A and B). In this patient the pulmonary changes are nonspecific and the regression under steroid therapy could be coincidental, but it is somewhat suggestive that the pulmonary changes may be related to an underlying hypersensitivity.

B. Disseminated lupus erythematosus.

Case 4: A 40 year old woman with butterfly rash on the face, signs of systemic illness, mild leukopenia and reversal of albumin-globulin ratio in plasma revealed evidence of pneumonitis and atelectasis in both pulmonary bases (Fig. 4). This combination has been termed "atelectasing pneumonitis" and is not entirely specific, but when a systemic disease is present, it is in favor of disseminated lupus erythematosus. Positive LE cell test and skin biopsy provided further confirmation.

Case 5: An adult woman with a butterfly rash on the face, history of photosensitivity and recurrent episodes of pneumonia had laboratory findings of telescopic urinary sediment, elevated ESR, reversal of A-G ratio and positive LE cell test in peripheral blood and bone marrow. A series of roentgenograms of the chest revealed bilateral interstitial pneumonitis, gradually enlarging heart and the development of pleuropericardial adhesions (Fig. 5). This sequence of changes, without evidence of cardiac failure and with involvement of serous surfaces, is in favor of a systemic disease, and strongly suggests or confirms the presence of disseminated lupus erythematosus.

C. Scleroderma.

Case 6: A 69 year old woman was admitted with complaints of tight thick skin on the forehead and temple, arthritis, dyspnea, edema of the lower extremities and flexion contracture of the fingers. Laboratory data revealed rbc in the urine, leukocytosis and left axis deviation on the electrocardiogram. Roentgenograms of the chest revealed nodular interstitial fibrosis in the middle and lower thirds of both lung fields, pneumonitis at the bases and pleural effusion, combined with enlargement of the left ventricle without signs of cardiac failure (Fig. 6A, B and C). This combination of changes is in favor of a systemic disease and is specifically suggestive of scleroderma.

Case 7: A 51 year old man complained of Raynaud's phenomenon, fever, cough and tight, thick skin over the forehead. Investigations for tuberculosis were negative. Roentgenograms of the chest revealed extensive fibrosis and ring-like shadows in both upper lobes with biiateral basal emphysema and pleural thickening at the left base (Fig. 7). This is an exceptional example of scleroderma in that the fibrosis and ring-like shadows occurred in the upper lobes, and lead to a suspicion of pulmonary tuberculosis. This combination of findings more commonly occurs in the middle and lower lung fields, but when tuberculosis is excluded, the appearance is strongly in favor of scleroderma.

D. Dermatomyositis.

Case 8: A 58 year old woman complained of muscle pain and stiffness, intermittent fever and erythematous rash on the face. Laboratory data revealed albumin in the urine and negative LE cell test. Roentgenographic examination of the chest revealed bilateral interstitial fibrosis and emphysema (Fig. 8). These findings are not diagnostic alone. When combined with calcification in the soft tissues the differential diagnosis of scleroderma and dermatomyositis should be entertained. The presence of the latter was confirmed by biopsy in this patient.

Case 9: A seven and one-half year old boy complained of red rash on the nose, anorexia, irritability, low grade fever, pain in the legs, easy fatiguability and swelling in the periorbital areas. Physical examination revealed temperature 99.6° F., pulse 120, palpable axillary and cervical nodes, grade II systolic murmur along the left sternal border, split second pulmonic sound, enlarged liver and contraction and atrophy of the muscles of the extremities. Laboratory data revealed positive urinary albumin and reversal of the A-G rtaio. No LS cells were found in the blood.

Roentgen examinations: February 11, 1955: chest negative. April 30, 1955: slight cardiac enlargement, minimal bilateral interstitial changes (Fig. 9A). November 28, 1955: increased cardiac enlargement, bilateral interstitial pneumonitis. January 14, 1956: heart larger, increase in bilateral interstitial pneumonitis (Fig. 9B). January 27, 1956: massive atelectasis left lung, interstitial and bronchopneumonia in right lung (Fig. 9C).

Treatment with cortisone, metacortone and testosterone were ineffective. Autopsy (January 27, 1956) revealed massive atelectasis left lung, interstitial and bronchopneumonia right lung, fibrinoid deposits in alveolar walls and dermatomyositis.

In this patient the gradual development of nonspecific cardiac enlargement and bilateral interstitial pneumonitis without signs of cardiac failure indicate the possibility of a collagen disease and are strongly confirmatory when considered with

other clinical and laboratory signs. The roentgen signs are not of further differential diagnostic value and could be seen in any of the collagen disorders. Biopsy or autopsy is then necessary to establish the diagnosis of dermatomyositis. The terminal atelectasis of the left lung is unusual and not of definite diagnostic aid.

Case 10: A 39 year old woman complained of general debilitation, dysphagia, weakness and soreness of the muscles of the upper extremities, skin rash and arthralgia. Physical examination revealed pronounced weakness and atrophy of the shoulder and upper arm muscles, and erythematous patchy skin lesions on the posterior aspect of the neck, back and dorsum of the hands. Laboratory data revealed normal urine, ESR 49 mm. per hour, negative LS cell test. Skin and muscle biopsy: dermatomyositis.

Roentgen examinations: June 7, 1955: chest negative. February 1, 1956: chest negative. February 12, 1956: bilateral interstitial pneumonitis. March 29, 1956: heart normal or slightly enlarged, increase in bilateral interstitial pneumonitis (Fig. 10). April 2, 1956: pneumonitis resolving. April 16, 1956: enlarged heart, bilateral basal bronchopneumonia, probable pulmonary edema.

In spite of treatment with cortisone and penicillin the patient developed a progressive anemia, cardiomegaly, thrombophlebitis and electrolyte imbalance. She expired on May 11, 1956. Autopsy refused.

In this patient the roentgen signs developed relatively late and were largely confirmatory. The development of bilateral interstitial pneumonitis is not diagnostic, especially when it occurs prior to the development of cardiac enlargement. The progressive anemia and cardiac enlargement were accompanied by the onset of pulmonary edema and basal bronchopneumonia which obscures the roentgen diagnostic picture.

E. Rheumatic pneumonitis.

Case 11: A 23 year old woman complained of fever, dyspnea, cough and chest pain of four years' duration. Clinical and laboratory data suggested the presence of rheumatic heart disease with an acute exacerbation of rheumatic fever. Roentgenographic examination of the chest revealed generalized dilatation of the cardiac silhouette, bilateral pneumonitis in the middle and lower lung fields and bilateral pleural effusion, without evidence of peripheral pulmonary vascular engorgement or pulmonary edema (Fig. 9), a combination strongly in favor of rheumatic pneumonitis (confirmed by autopsy).

F. Overlapping or transitional form.

Case 12: A 32 year old woman complained of fatigue, multiple food allergies and a red, scaling erythematous rash on the face and body. Laboratory examination revealed telescopic urinary sediment, reversal of A-G ratio, elevated ESR and eosinophilia. On admission the roentgenogram of the chest was normal but later there was left basal pneumonitis and pleural effusion, and plain roentgenograms of the abdomen revealed adynamic ileus. On autopsy there were renal changes typical of disseminated lupus erythematosus and vascular lesions in various organs like those of polyarteritis.

Clinical and laboratory data in this patient suggested the presence of a collagen disease with changes which could be found in either polyarteritis or disseminated lupus erythematosus. The findings on autopsy indicate that this patient presents an overlapping or transition between the two conditions. In retrospect one might reason that the roentgen changes in the chest and abdomen could be caused by either condition but were evidently based on the polyarteritis.

SUMMARY

Clinical and laboratory data are cited which may lead one to suspect the presence of a collagen disease, and diagnostic points are presented to aid in the differential diagnosis of the various collagen disorders.

Clinical and roentgenographic manifestations of involvement of thoracic structures by collagen diseases is more common than has been stressed in the medical literature, including such relatively uncommon conditions as dermatomyositis.

Roentgen abnormalities in the chest may quite often lead one to suspect the presence of a collagen disease, and certain combinations or sequential changes may even aid in the differential diagnosis of the various conditions.

Roentgenographic and pathologic data support the separation of rheumatic pneumonitis as a specific entity.

RESUMEN

Se mencionan los datos clínicos y los de laboratorio que pueden conducir a la sospecha de una enfermedad a la colágena y se hacen consideraciones sobre diagnóstico diferencial.

Las manifestaciones clínicas y radiológicas de compromiso de los órganos torácicos por enfermedades colágenas son más comunes de los que ha hecho notar en la literatura médica, incluyendo tales afecciones tan poco comunes como la dermatomiosistis.

Las anormalidades del tórax pueden muy a menudo hacer sospechar la presencia de

afección de la colágena y ciertas combinaciones o cambios subsecuentes pueden ayudar a la diferenciación de varias de esas afecciones.

Los datos radiológicos y patológicos apoyan la separación de la neumonitis reumática como una entidad especifica.

RESUME

L'auteur cite les faits cliniques et les résultats de laboratoire qui peuvent conduire à suspecter l'existence d'une maladie du collagène. Il propose des éléments de diagnostic qui peuvent aider au diagnostic différentiel des différents troubles du collagène.

Les manifestations cliniques et radiologiques d'atteinte thoracique due aux maladies du collagène sont plus communes que ne le montre la littérature médicale, y compris des états relativement inhabituels tels que la dermatomyosite.

Les anomalies radiologiques du thorax peuvent assez souvent conduire à suspecter l'existence d'une maladie du collagène, et certaines associations ou évolution des altérations peuvent même aider au diagnostic différentiel des diverses formes de ces affections.

Les faits radiographiques et anatomo-pathologiques permettent d'isoler la pneumonie rhumatismale et de la considérer comme une entité spécifique.

ZUSAMMENFASSUNG

Es werden klinische und Laboratoriumswerte angeführt, die Veranlassung geben können zur Vermutung, dass eine Bindegewebskrankheit vorliegt, und es werden diagnostische Gesichtspunkte vorgetragen als Hilfe bei der Differentialdiagnose der verschiedenen Störungen des Bindegewebes.

Klinische und röntgenologische Manifestationen einer Beteiligung der thorakalen Strukturen bei Bindegewebskrankheiten sind häufiger als in der medizinischen Literatur herausgearbeitet wurde, einschliesslich solcher relativ ungewöhnlichen Zustände wie Dermatomyositis.

Röntgenologische Abnormalitäten im Thorax können ziemlich oft zu der Vermutung Veranlassung geben, dass eine Bindegewebskrankheit vorliegt, und gewisse Kombinationen oder aufeinander folgende Veränderungen können sogar eine Hilfe sein für die Differentialdiagnose der verschiedenen Krankheits zustände.

Röntgenologische und pathologisch-anatomische Angaben stützen die Abgrenzung der rheumatischen Pneumonitis als einer ganz spezifischen Krankheitseinheit.

References will appear in author's reprints.

SECTION ON CARDIOVASCULAR DISEASES

Current Status of Surgical Treatment of Ventricular Septal Defect*

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Until the past few years repair of congenital septal defects was possible for only a selected number of lesions utilizing usually an exploring finger inside the heart for digital guidance. By means of technical ingenuity and utilization of certain anatomic characteristics of the defect, sutures were passed through the heart for the repair. Such methods were satisfactory for many atrial septal defects particularly those involving the region of the septum secundum or foramen ovale. A similar method which was suggested for defects of the ventricular septum met with limited success.[2] An example of the occasional good result obtained with closed methods was one patient, 18 months old, previously reported in 1955 in whom transventricular suture fixation of a ventricular septal defect was performed. Two years later cardiac catheterization was repeated revealing no residual intraventricular shunt and normal pulmonary arterial pressures (Table I). Roentgenograms of the chest also indicated improvement (Fig. 1). Although results of this type are obviously gratifying the technic was unreliable since the repair lacked the precision provided by direct vision.

In 1954 Lillehei and his associates[5] reported the first successful cases of open heart surgery using artificial maintenance of circulation. In these initial cases a donor was used as a biologic oxygenator for the venous blood and controlled cross circulation was established between patient and donor. Meanwhile Kirklin and associates[7] modified the Gibbon vertical screen oxygenator and demonstrated that oxygenation as well as controlled circulation of blood could be accomplished artificially with an acceptable risk. DeWall and Lillehei[4] soon substituted a mechanical oxygenator in their circuit. These significant events were highly important in opening a new phase of cardiac surgery in which open cardiotomy provides the means of direct repair of a wide variety of cardiac lesions many of which were previously considered incorrectible. Approximately four years after these initial clinical efforts proved successful this report is being prepared based largely upon observations made in our own series of 130 patients operated

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**From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and the surgical services of the Jefferson Davis, Methodist, and Veterans Administration Hospitals.

TABLE I†

	Oxygen Saturation (Per cent)		Pressure (mm. Hg)	
	Before Operation*	After Operation**	Before Operation	After Operation
Inferior Vena Cava	53	75	0	—
Superior Vena Cava	77	82	0	—
Right Auricle (mid)	70	80	0	5 (mean)
Right Ventricle (apex)	87	80	68/0	35/0
Right Ventricle (out)	82		62/0	
Main Pulmonary Artery	87	80	60/12	35/20
Right Pulmonary Artery	90	82	54/12	32/16
Brachial Artery				90/50

*November 18, 1954

**December 11, 1956

†Cardiac catheterization data in an eighteen month old patient made before operation and two years after repair of a ventricular septal defect using a closed technic of transventricular suture. Although the defect is completely closed the technic has been replaced by open cardiac procedures.

upon with a diagnosis of ventricular septal defect in which a pump oxygenator was used for cardiopulmonary bypass.

Types of Defects

Ventricular septal defects occur in a variety of locations. Primarily for the sake of simplicity and consistency we have classified the defects into Types I to IV (Fig. 2 a-d). The typical defect of the membranous septum is the most common occurring in 102 out of 130 cases, (78 per cent) (Fig. 2b). In membranous defects the aortic valve is in close proximity to the upper margin and in some instances the annulus of the aortic valve overrides the septum. The remainder of the defects (Types I, III, and IV)

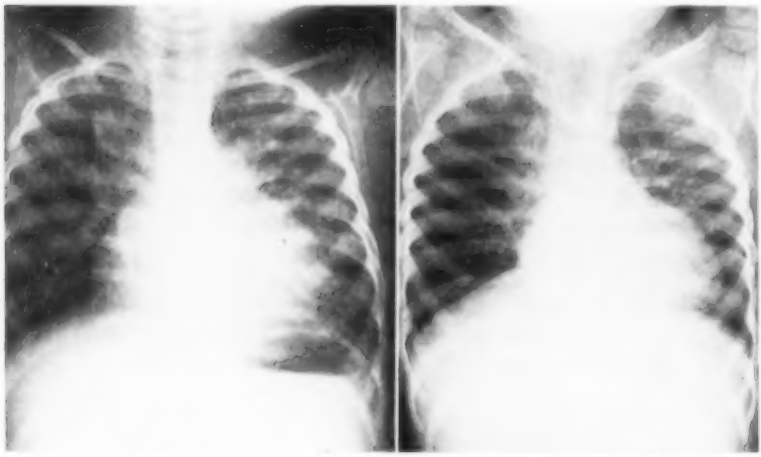

FIGURE 1A FIGURE 1B

Figure 1: Roentgenograms of chest made before (a) and six months after (b) operation in same patient as in Table I. The pulmonary vascular markings are reduced and heart size is proportionately smaller.

involve the muscular portion of the ventricular septum. If the lesion is in the outflow tract above the crista supraventricularis, it is referred to as Type I (Fig. 2a). Usually these lesions are small and surrounded by fibrous tissue. Type III defects are located close to the annulus of the tricuspid valve behind the posterior leaflet. Usually chordae tendineae overlie the defect when viewed from the right ventricular side of the septum (Fig. 2c). Type IV defects are located in the muscular portion of the ventricular septum often near the attachments of the papillary muscles (Fig. 2d). Frequently these defects are multiple fenestrations which are difficult to identify in the spaces between the carnae trabeculae.

The term "common ventricle" is applied to defects in which practically the entire ventricular septum is absent (Fig. 3). Chordae tendineae and papillary muscles are suspended across the large defect which joins the two otherwise normal ventricles into a common chamber. Common ventricle is not the same lesion as the so-called single ventricle in which a rudimentary ventricular chamber is usually present. Single ventricle is not a correctible type of lesion. A unique form of ventricular septal defect which is uncommon but not rare produces a left ventricular to right atrial shunt and is associated usually with a cleft in the septal leaflet of the tricuspid valve (Fig. 4). This defect is particularly interesting because cardiac catheterization reveals a large left to right shunt at the right atrial

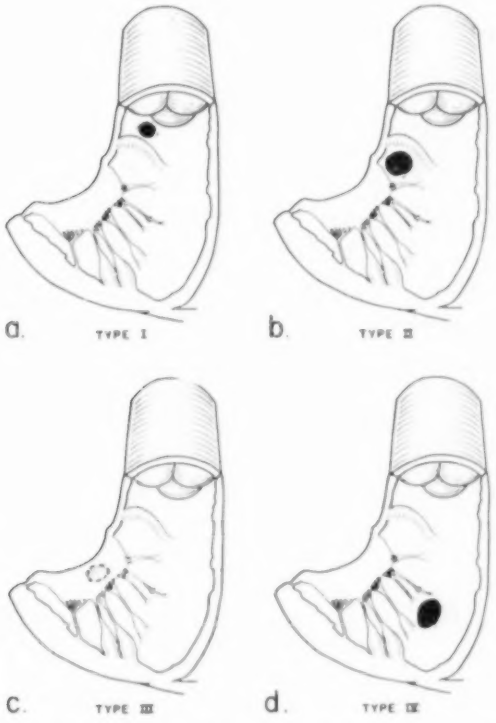

FIGURE 2: Drawings of interventricular septum showing location of various ventricular defects referred to in this report. Among 130 patients operated upon 7 were Type I, 102 were type II, 8 were Type III, and 6 were Type IV.

level with murmur and physical findings suggestive of a ventricular defect. Identification of a ventriculo-atrial defect is important since repair through the right atrium may provide the optimum means of repair.

Surgical Technic

The pump oxygenator system employed in our cases consists of a stainless steel oxygenator incorporated in a system with a complete occlusive type of pump.[3] Oxygenation of blood is accomplished employing the bubble diffusion principle, oxygen being dispersed through a perforated plate in the bottom of a diffusion column containing venous blood. Defoaming is obtained by use of Dow Corning Antifoam A applied to a disposable stainless steel sponge. In addition to this type of oxygenator we have employed a completely disposable plastic device in some cases with good success. The disposable oxygenator described by Gott and associates[5] is convenient and inexpensive. Future modifications and improvements of this oxygenator should facilitate and simplify open heart operations considerably. We have noted no significant differences in the function of the roller type pumps (De Bakey-Mark) and the multiple lever pumps (Sigmamotor) when both are used with complete occlusion of the tube. In most patients flow rates of 35-50 cc./Kg. body weight/minute were used. In infants at least 50

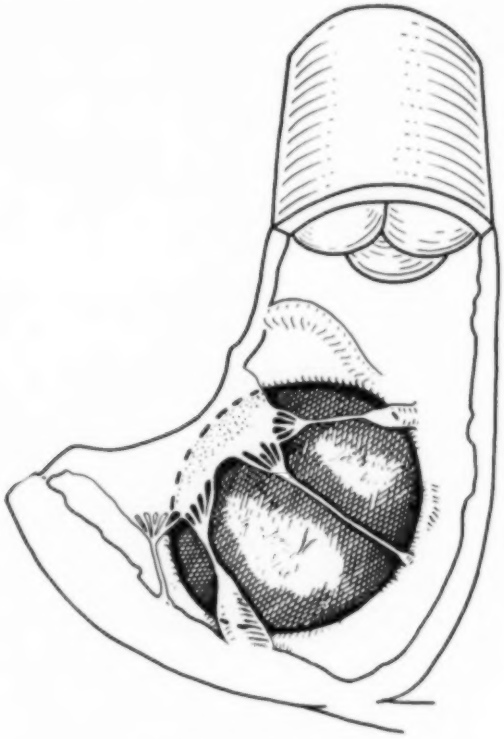

FIGURE 3: Drawing showing large ventricular defect producing a common ventricle. Papillary muscles and chordae tendineae are suspended across the defect.

cc./Kg. was administered and for most adults or older children 35 cc./Kg. was the selected rate of flow. Most perfusions for ventricular septal defect were less than 20 minutes in duration and some were less than 10 minutes.

Blood for priming the pump oxygenator system was collected on the day preceding operation into 500 cc. bottles containing 25 mg. Heparin and 60 cc. of physiologic saline in 5 per cent glucose solution.[1] Between four and six donors were used depending upon the size of the patient. Storing of blood for twenty-four hours has been convenient in these operations since it permits unhurried collection and processing for operation.[1] Experimental and clinical studies on stored heparinized blood indicate that this method of blood procurement is entirely satisfactory. Just prior to bypass the refrigerated blood is warmed to body temperature before filling the oxygenator. The patient receives Heparin 1.5-2.0 mg./Kg. body weight before the cannulations are done. After bypass the Heparin is neutralized with Protamine sulfate 2.0-2.5 mg./Kg. Bleeding problems after operation are rare and usually associated with some technical error and failure to obtain meticulous hemostasis. True bleeding diatheses may occur, but in our experience these are probably related to capillary damage due to an unsatisfactory perfusion or complicated prolonged operation. Increased venous pressure due to a failing heart may also increase bleeding from the thoracotomy incision. In these instances clotting mechanism is usually within the limits of normal.

Anesthesia

Light general anesthesia with deliberate hyperventilation was used to provide a high tension tissue store of oxygen by nitrogen washout. The resulting respiratory alkalosis compensated for the metabolic acidosis produced by low flow perfusion.[6] It was not necessary to add any anesthetic agent or carbon dioxide to the oxygenator during cardiopulmonary bypass.

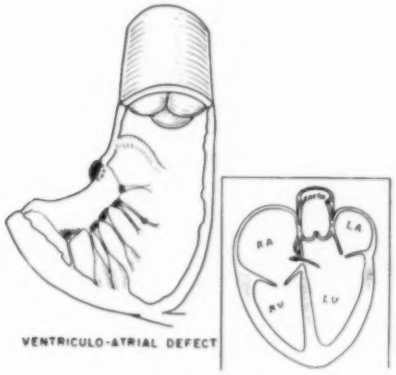

FIGURE 4

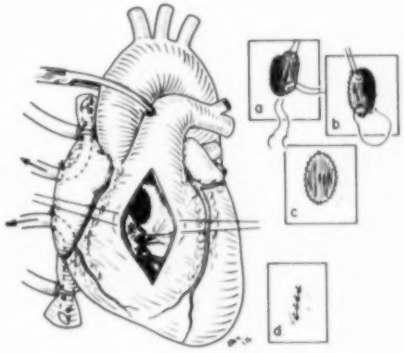

FIGURE 5

Figure 4: Drawing showing an unusual type of ventricular septal defect producing a left ventricular to right atrial shunt (Inset). In this defect the communication with the right atrium lies above the tricuspid annulus and is usually associated with an anomalous cleft tricuspid valve. Ventriculo-atrial defects were encountered in 4 patients. —*Figure 5:* Drawing showing method of exposure of ventricular septal defects using transventricular approach. In large defects on the membranous septum the opening is closed with a Dacron knit patch using silk sutures (a, b, c). In small defects a direct suture repair is satisfactory (d.)

Curare was administered prior to bypass to eliminate striated muscle contraction and minimize metabolic acidosis. In our cases use of sodium bicarbonate or other alkaline solutions have not been necessary after operation since the mild degree of acidosis sometimes encountered is rapidly corrected after the operation by adequate ventilation and fluid replacement.

Surgical Repair

A bilateral thoracotomy entering usually the fourth intercostal space and transecting the sternum is the usual incision employed for ventricular defects. Recently a median sternotomy has been used in a few patients and provides good exposure of the heart and appears to be well tolerated by the patient. In most instances it is not necessary to open the pleural spaces when the sternotomy is employed. Cannulations of the superior and inferior vena cava are made by passing plastic catheters through purse string sutures in the right atrium. Return of oxygenated blood is made into a common femoral artery. This completes the extracorporeal circuit. Insertion of a cannula into the left atrium removes blood returning from bronchial vessels and reduces considerably the blood which enters the left ventricle. This catheter is connected to the inflow of the pump oxygenator.

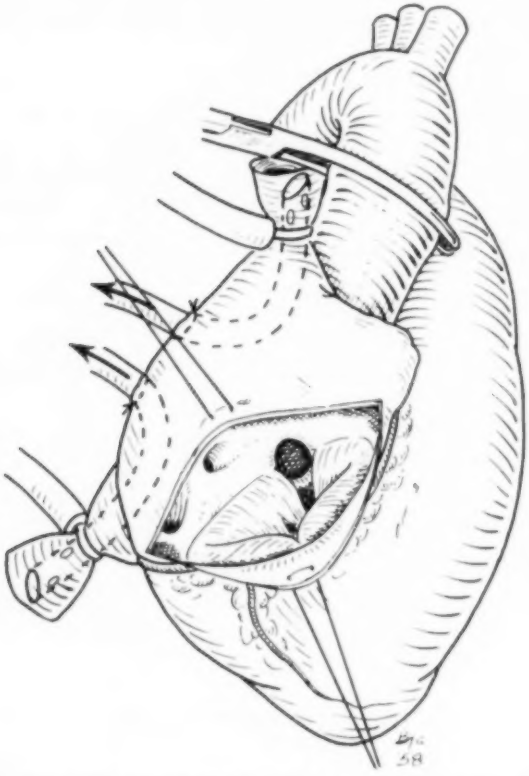

FIGURE 6: Drawing showing method of repair of ventriculo-atrial defect using transatrial approach. The defect is located in the membranous septum and is associated with a cleft tricuspid valve. This approach is also useful for Type III defects of the ventricular septum in which instance the tricuspid valve leaflet must be incised.

With the pump oxygenator functioning and the caval inflow to the heart occluded exposure of the defect is obtained by incising the ventricle in the direction of the outflow (Fig. 5). Exposure of the defect is facilitated by temporary occlusion of the ascending aorta which reduces coronary venous return. Intermittent occlusion of the aorta for two to five minute periods permits continued myocardial contractions, and if injury to the A-V conduction bundle occurs it can be recognized immediately. Under these circumstances removal and replacement of the offending suture may prevent a total A-V block after operation. Induced cardiac arrest is not used at the present time in our cases because of the frequency of conduction complications encountered. For example, in 72 patients with various types of congenital defects in whom Potassium citrate arrest was used 17 (24 per cent) developed ventricular fibrillation and 8 (47 per cent) could not be defibrillated with electric shock.[6] In the first 68 patients operated upon using intermittent aortic occlusion ventricular fibrillation occurred in 11, and in three of these defibrillation was not effective. With increasing experience with the technique of intermittent occlusion of the ascending aorta opening the clamp when the myocardium becomes cyanotic or feeble, we have had an extremely low incidence of ventricular fibrillation. Moreover, omission of the arrest technique shortens the necessary period of perfusion and myocardial contractions are more forceful after repair of the defect.

Actual repair of the defect depends upon the size and location of the opening. In our experience defects of the membranous ventricular septum (Type II) are four times as common as all others combined. In the membranous defect closure should be obtained without producing tension on the suture line. This can best be obtained by suturing a patch of synthetic material into the opening with continuous and interrupted silk sutures (Fig. 5). Although compressed Ivalon was a satisfactory material for this purpose, knitted Dacron of the type used for vascular grafts has been used recently and may be superior. If the septal defect is small or surrounded with fibrous tissue, closure with interrupted silk sutures is performed.

Some defects may be difficult to repair through the ventricle, and exposure through the right atrium may be more practical (Fig. 6). This is particularly true of the so-called ventriculo-atrial defects (Fig. 4) and Type III defects (Fig. 2c). Exposure of the ventriculo-atrial defects is excellent by the transatrial approach since a cleft in the septal leaflet of the tricuspid valve is common. In Type III defects incision of the posterior leaflet of the tricuspid valve may be necessary, but even this is easier in many instances than attempting to deal with the multiple chordae tendineae which interfere with repair using the transventricular approach. Repair of a common ventricle type of defect requires the use of a large patch of synthetic material. This lesion has been successfully repaired in two out of three cases in our experience. Corrected transposition was present in four patients with ventricular septal defect. Repair of the septal defect in the presence of a corrected transposition is made somewhat difficult by the unusual distribution of valvular attachments and chordae tendineae in the right ventricle. Successful repair of a ventricular defect was accomplished in three patients with corrected transposition of the great vessels. Congenital A-V block was present in three patients with corrected

transposition and ventricular defect and persisted after operation without causing significant cardiac disturbance.[9] It has been suggested by us that this combination represents a clinical triad.

Results

From January 1956 to March 1958, a total of 130 patients were operated upon with a diagnosis of isolated ventricular septal defect. During this period this lesion represented the most common type of cardiovascular operation in which the pump oxygenator was used for temporary cardiopulmonary bypass (Table I). A number of factors determined survival in these patients with ventricular defects, including age, severity of pulmonary vascular changes, and presence of associated cardiovascular lesions. Analysis of the patients according to the influence of age on survival indicates that operation during infancy carries a high operative risk (Table II). In our series the over-all mortality was 18.4 per cent but more than 60 per cent of deaths occurred in patients less than two years of age, the infants representing only 30 per cent of the entire series. Among 71 patients between the ages of two and 14 years there were five deaths or a mortality of 7 per cent. A salvage of 70 per cent of patients less than two years of age represents a particularly gratifying experience with infant

TABLE II
CARDIOVASCULAR LESIONS OPERATED UPON USING TEMPORARY CARDIOPULMONARY BYPASS BEFORE APRIL 15, 1958

Lesion	*Number*
Ventricular septal defect	130
Atrial septal defect (ost. II)	55
Atrial septal defect (ost. I)	10
Atrio-ventricularis communis (partial)	9
Atrio-ventricularis communis (complete)	9
Tetralogy of Fallot	23
Aortic stenosis (calcific)	17
Aortic stenosis (congenital)	15
Aortic arch aneurysm	13
Pulmonic stenosis (infundibular)	9
Pulmonic stenosis (valvular)	7
Total anomaly pulmonary venous drainage	7
Mitral stenosis (recurrent)	6
Transposition of great vessels	6
Mitral insufficiency	4
Cardiac myxoma (Lt. atrium—2) (Rt. atrium—1)	3
Myocardial infarction (Lt. ventricular aneurysm—2) Perforation ventricular septum—1)	3
Traumatic lesions (Stab wound—aorto-ventricular fistula—2) (Blunt injury—ruptured papillary muscle—1)	3
Aortic insufficiency	3
Aortico-pulmonary septal defect	2
Miscellaneous congenital lesions	11
Total	345

patients with ventricular septal defect because of the grave prognosis without operation.

Risk of operation was increased by the presence of pulmonary hypertension. The most severe postoperative complications and morbidity occurred in patients in whom pulmonary arterial pressure was more than 70 per cent of systemic arterial pressure. Indeed, the majority of deaths occurred in patients with increased pulmonary resistance secondary to pulmonary arteriolar changes. Not a single death occurred in patients in which pulmonary arterial pressure was less than 50 per cent of systemic pressure. Nevertheless, the fact that at least 15 patients in whom pulmonary and systemic pressures were equal survived operation is indication enough that operation is feasible even under these circumstances. Although frank cyanosis, polycythemia and clubbing of nails was not present in any of the patients, evidence of balanced or partial reversal of the ventricular shunt was present in many. Peripheral arterial saturation of 80 per cent while the patient was breathing room air was not a contraindication for operation. In most such patients breathing 100 per cent oxygen eliminated the right to left shunt, and peripheral arterial oxygen saturation rose to 95 to 98 per cent. After operation pulmonary arterial pressure showed a progressive and substantial decrease at follow-up cardiac catheterization. Apparently there is evidence of regression or healing of the pulmonary vascular lesion after closure of a ventricular septal defect.

Associated cardiovascular anomalies were demonstrated in many of these patients, the most common being patent ductus arteriosus. This lesion was present in eight patients and was repaired in each instance before bypass was started. Among the associated defects encountered were coarctation of the aorta, atrial septal defect, pulmonary valvular or infundibular stenosis, ruptured papillary muscle of tricuspid valve, right aortic arch, overriding aorta, and corrected transposition of the great vessels. Whenever it was considered necessary and practical the associated defects were corrected at the time of operation and sometimes during bypass. In some cases, however, the associated defect was not considered to be significant and no repair was attempted. Of interest was one patient four months of age who survived closure of a ventricular septal defect six weeks after a coarctation of the aorta and patent ductus arteriosus had been repaired.

TABLE III

TABLE SHOWING RESULTS OF OPERATION FOR VENTRICULAR SEPTAL DEFECT ACCORDING TO AGE OF PATIENT. AMONG 71 PATIENTS BETWEEN TWO AND FIFTEEN YEARS OF AGE THERE WERE 5 DEATHS OR 7 PER CENT MORTALITY

		Results	
Age (yrs.)	*No. Patients*	*Deaths*	*Per Cent*
0 - 1 (youngest 2 months)	29	12	41
1 - 2	10	3	30
2 - 5	32	2	6
5 - 14	39	3	7
14 -	20	4	20
Total	130	24	18.4

Three in this series were operated upon because of recurrence of the septal defect. In two the second operation was successful but one seven month old expired after the second operation. Reoperation should be strongly considered if recurrence is suspected since secondary repair is feasible. Cardiac catheterization should be performed in all patients with suspected recurrence of ventricular defects. Systolic murmurs may occur in many patients after operation even in the absence of a recurrence. Persistent pulmonary hypertension may cause congestive failure after operation even if the septal defect has been completely repaired.

DISCUSSION

Certain observations on the problem of management of ventricular septal defects can be made on the basis of our experience with 130 cases. If in the selection of patients for operation all patients less than two years of age were eliminated, results of operation could be significantly improved. Exclusion of infant patients would represent, however, a serious injustice because prognosis is always grave in this age group. Congestive failure and respiratory complications lead to a high mortality among infants with this disease and often repair of the defect becomes an urgent problem. If the response to a strict and careful medical program is not favorable and the condition of the patient continues to be poor, operation must be considered regardless of age or size of the patient. If at all possible, however, operation should be postponed until the patient is 18 months of age at least since the risk of operation is so much less. Older patients between two and 15 years of age provide a good risk for operation with a mortality of 7 per cent in our patients regardless of other factors, including in many pulmonary hypertension.

As the risk of operation becomes progressively lower with increasing surgical experience, indications for operation should become broader to avoid the complications which plague these patients throughout life. Certainly operation in elective cases with significant left to right shunts should be done before bacterial endocarditis, congestive failure, or pulmonary hypertension appear. Within the next few years the presence of an uncomplicated ventricular septal defect will be accepted as sufficient indication to recommend surgical repair.

At present the principal contraindication to operation lies in the presence of severe pulmonary vascular resistance leading to reversal of the intracardiac shunt. The presence of a bi-directional shunt with pressures in the pulmonary artery and aorta being approximately equal does not contraindicate operation. Indeed peripheral cyanosis of mild degree was present in many patients in this series. Peripheral arterial oxygen saturation while breathing room air was 84 per cent in several patients and good results followed repair of the defect. Patients with moderate to severe cyanosis associated with polycythemia and clubbing of the nails were not accepted for operation and were usually considered to be examples of Eisenmenger's complex. Study of this type of patient is important since it is possible that many could be brought through operation. Gradual elimination of the intracardiac shunt by using a perforated patch in the repair may provide some assistance in these patients. The perforations would close slowly in the weeks following operation providing needed time for gradual healing of the pulmonary vascular lesions. Another method of providing gradual elimination of the shunt would be to create an artificial patent ductus arteriosus using a vessel graft between the pulmonary artery and aorta at the time of closure of the ventricular defect. Subsequently the extracardiac shunt could be eliminated at another operation. These methods are currently being tested in several clinics and the results may provide assistance with this problem. Already it has been demonstrated that postoperative complications can be reduced in patients with pulmonary hypertension by inhalation of high oxygen concentrations provided in many instances by tracheostomy and mechanical assistors of respiration. Discovery of an effective drug for reduction of pulmonary vascular resistance would be most welcome as an adjunct in this problem.

ADDENDUM

On April 25, 1959, a total of 585 patients had undergone operations using temporary cardiopulmonary bypass. Of these 193 had isolated ventricular septal defects. Six deaths occurred among these 63 patients, 2 being infants less than 18 months of age and the other 4 having severe pulmonary hypertension. The opinions expressed in the paper have not changed significantly in the interim. Risk of operation depends primarily upon methods of selection of patients for surgical repair. Small infants and patients with advanced pulmonary vascular changes account for the mortality of 15 per cent in the entire series. In favorable cases the expected surgical mortality should be less than 2 per cent.

SUMMARY

Surgical repair of ventricular septal defect is now an established precedure in cardiac surgery using a pump oxygenator for temporary cardiopulmonary bypass. From a collected series of 345 patients undergoing operation during bypass for a variety of congenital and acquired cardiovascular lesions, 130 had isolated ventricular septal defect. From this experience ventricular defects appear to be the most common congenital cardiac defects requiring open heart surgery.

Analysis of the experience reveals highly satisfactory results among those between ages two and 15 years. Among 71 patients in this age group there were five deaths or a mortality of 7 per cent. Risk of operation during infancy is substantially higher. However, a salvage of 70 per cent of patients less than two years of age justifies operation even in these critically ill patients.

Pulmonary hypertension is frequently associated with ventricular septal defect. As pulmonary vascular resistance increases in these patients, reversal of the intracardiac shunt may lead to cyanosis. The extent of pulmonary vascular changes influences the risk of operation. Although patients with a so-called Eisenmenger's complex associated with cyanosis, clubbed nails, polycythemia, and right ventricular hypertrophy are not satisfactory candidates for surgical treatment, we have operated successfully upon a number of patients with balanced or combined left to right and right to left shunts. Future developments may help control the physiologic effects of the increased pulmonary vascular resistance and thus make possible operative correction in almost all patients with ventricular septal defects.

RESUMEN

La reparación quirúrgica de un defecto septal ventricular en un procedimiento ya establecido en cirugía cardiaca usando una bomba con oxigenador para la desviación temporal dela corriente sanguínea.

De una serie colectada de 345 enfermos sometidos a operación mientras se usó la desviación de la corriente sanguínea para una variedad de lesiones congenitas y adquiridas cardiovasculaes,130 tenían defectos del tabique aislados. Según esta experiencia los defectos ventriculares parecen ser los más comunes defectos congénitos que requieren cirugía de corazón abierto.

El análisis de la experiencia revela resultados muy satisfactorios en los de edad entre 2 y 15 años. Entre 71 enformos en est edad hubo 5 muertes o sea 7 por ciento. El riesto de operación durante la infancia es en general mayor. Sin embargo un rescate del 70 por ciento de enformos de menos de dos años de edad justifica la operación aún en estos enfermos tan gravemente afectados.

La hipertensión pulmonar se asocia frecuentemente con los defectos septales ventriculares. A medida que la resistencia vascular aumenta en estos enfermos, la inversión del "shunt" intracardiaco puede conducir a la cianosis. La extensión de los cambios vasculares influye en el riesgo de la operación. Aunque los enfermos con el llamado complejo de Eisenmeger, asociado con cianosis, uñas abombadas, policitemia e hipertrofia ventricular derecha, no son condidatos satisfactorios para la cirugía hemos operado sobre cierto número de estos casos con intercomunicaciones de izquierda a derecha o inversas, equilibradas y esto se ha hecho con éxito.

Los progresos futuros pueden ayudar a controlar los efectos fisiológicos del aumento de la resistencia vascular y así hacer posible la corrección operatoria en casi todos los enformos con defectos del tabique ventricular.

RESUME

La chirurgie réparatrice d'un défaut de la paroi ventriculaire est maintenant un procédé tout à fait au point en chirurgie cardiaque, en utilisant une pompe oxygénatrice pour l'alimentation cardiopulmonaire momentanée. Sur une série de 345 malades soumis à l'intervention pour différentes lésions cardiovasculaires congénitales ou acquises, 130 étaient porteurs d'une altération isolée de la paroi ventriculaire. D'après cette expérience, les altérations ventriculaires semblent être les altérations cardiaques congénitales les plus fréquentes, nécessitant une intervention à coeur ouvert.

L'analyse de l'expérience fournit des résultats très satisfaisants parmi les malades âgés de 2 à 15 ans. Sur 71 malades de cet âge, il y eut 5 décès, c'est-à-dire une mortalité de 7%. Le risque de l'opération pendant la petite enfance est substantiellement plus élevé. Cependant le sauvetage de 70% de malades âgés de moins de deux ans justifie l'intervention même chez ces malades dont l'état est critique.

L'hypertension pulmonaire est fréquemment associée à un défaut de la paroi ventriculaire. Comme la résistance vasculaire pulmonaire augmente chez ces malades, l'inversion du shunt intracardiaque peut amener la cyanose. L'étendue des altérations vasculaires pulmonaires influence le risque opératoire. Bien que pour les malades atteints du complexe dit d'Eisenmenger associé à la cyanose, avec déformation onguéales, polycythémie et hypertrophie ventriculaire droite, le traitement chirurgical ne donne pas de résultats satisfaisants, nous avons opéré avec succès un nombre de malades atteints de shunts équilibrés ou associés de gauche à droite et de droite à gauche. Des observations ultérieures peuvent aider à pallier aux effets physiologiques de l'augmentation de la résistance vasculaire pulmonaire et rendre ainsi possible une correction chirurgicale chez presque tous les malades atteints de défauts de la paroi ventriculaire.

ZUSAMMENFASSUNGEN

Operative Beseitigung eines Kammerscheidewanddefektes ist jetzt eine gut fundierte Massnahme in der Herzchirurgie, bei der man einen Pumpen-Oxygenator bentzt für einen temporären Herz-Lungen-Kollateral-Kreislauf. In einer zusammengestellten Reihe von 345 Patienten mit Operation während dieses Kollateralkreislaufeswegen der verschiedensten angeborenen oder erworbenen kardiovaskulären Läsionen 130 einen isolierten Kammerscheidewanddefekt.

Auf Grund dieser Erfahrung scheinen die Kammerdefekte die häufigsten kongenitalen Herzfehler zu sein, die Operationen am offenen Herzen erforderlich machen.

Auswertung der Erfahrungen ergab höchst befriedigende Ergebnisse bei solchen Kranken zwischen dem 2. und 15. Lebensjahr.

Bei 71 Patienten in dieser Altersgruppe fanden sich 5 todesfälle, was einer Mortalität von 7% entspricht. Das Operationsrisiko im Kleinstkindalter liegt beträchtlich höher. Jedoch rechtfertigt die Rettung von 70% von Patienten unter 2 Jahren die Operation. Selbst bei diesen kritisch granken Patienten.

Pulmonale Hypertension ist häufig verknüpft mit Kammerscheidewanddefekten. Da der pulmonale Gefässwiderstand bei diesen Krankenwachst, kann eine Umkehr des intrakardialen Shunts zu Cyanosen führen. Das Ausmass der pulmonalen Gefassveränderungen beeinflusst das Operationsrisiko. Wenngleich Patienten mit einem sogenannten Eisenmenger-Komplex in Verbindung mit Cyanose, Uhrglasfingernägeln, Policythämie und hyperthrophie der rechten Kammer kein befriedigendes Material darstellt für die chirurgische Behandlung, haben wir eine Anzahl von Patienten mit ausgeglichenen order kombinierten Links-rechts und Recht—Links-Shunten erfolgreich operiert. Die Entwicklung der Zukunft wird dazu beitragen, mit dem physiologischen Effekt des erhöhten pumonalen Gefässwiderstandes fertig zu werden under macht so die operative Korrektur möglich bei fast allen Patienten mit Kammerscheidewanddefekten.

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The Effect of Forced Inhalation of Tobacco Smoke on the Electrocardiogram of Normal and Tobacco-Sensitized Rabbits*

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The purpose of this study was to determine the effect of tobacco smoke on the cardiovascular system of experimental animals sensitized to tobacco protein. Rabbits were chosen as the experimental animal since they usually lend themselves well to sensitization procedures; however, special technics had to be developed for the recording of satisfactory electrocardiograms on these animals. The experimental problem involved the subjection of these rabbits to the forced inhalation of cigar smoke and the simultaneous recording of electrocardiographic tracings. The series of animal studies to date (over 30) is not sufficiently large to warrant conclusions based on statistical data. However, the results are interesting enough to justify this presentation.

The pharmacologic effects of nicotine on the cardiovascular system are well recorded in standard text books of pharmacology and a comprehensive review of this subject has been published.[1] Briefly summarized, these include: vasoconstriction of the peripheral vascular bed mediated through the action of nicotine on the autonomic nervous system, and a resultant increase in heart rate and blood pressure as well as peripheral vasoconstriction which are probably secondary responses brought about by the stimulating action of nicotine on the central nervous system, the chemoreceptors of the carotid and aortic bodies, and the renal medulla. It is not surprising, therefore, that electrocardiographic changes or abnormalities on humans have been recorded following the smoking of tobacco. Among the striking changes noted in these electrocardiographic tracings have been those in the T-wave configuration[2, 3] which have been attributed to an increase in the work of the heart[2] as manifested by the increase in cardiac rate and blood pressure through the action of nicotine on the vagus and sympathetic ganglia[3] rather than through any direct effect on the coronary vasculature itself.[3, 4]

The immunologic specificity of tobacco as an antigen in hypersensitivity reactions has also been a subject of consideration and investigation. Details pertaining to this question have been reviewed and summarized by Harkavy[5] and by Lowell. Clinical suspicion for the existence of tobacco allergy was suggested by the demonstration of circulating reaginic antibodies against tobacco protein in humans according to the studies of Harkavy, Harkavy and Witebsky[6] and Peshkin and Landay. Experimental sensitization to tobacco protein as an antigen in rats was established by Harkavy[7] as proved by anaphylactic type challenge reactions of sensitized intestinal stripes utilizing the Schultz-Dale technic. An interesting and important finding in these sensitized animals was the development of gangrenous lesions of the extremities.

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The importance of tobacco and the effect of smoking in patients with thromboangiitis obliterans is an observation well known to clinicians and an attempt has been made to evaluate the possibility of an actual hypersensitivity to tobacco in these instances by the finding of a high percentage of positive skin test reactions using a tobacco protein challenging antigen.[8] A similar approach to the question of the possible role of tobacco hypersensitivity in angina pectoris and coronary artery disease in humans has been attempted by Harkavy,[5] again utilizing the skin test reaction to suggest the effect of tobacco, here, as an allergen.

An experimental approach to the further study of this question of tobacco hypersensitivity affecting the cardiovascular system has been considered in this paper concerned with a study of electrocardiographic recordings in normal and tobacco sensitized animals. It was felt that any detectable change in the normal function of the cardiovascular system might be reflected in the electrocardiograms of these experimental animals while subjected to the forced inhalation of tobacco smoke. We have attempted to determine any difference of response in normal and tobacco sensitized rabbits subjected to the identical challenge with the hope that results might contribute some evidence for or against a specific role of tobacco smoke as an antigen in experimentally induced alterations of cardiovascualr function. We have also attempted to determine whether or not these might arise on the basis of an immunologic reaction of hypersensitivity.

Sensitization Procedures: A tobacco protein extract was prepared by standard extracting procedures from commercial grade cured tobacco leaves of Pennsylvania and Connecticut stock used in the manufacture of cigars. This alkaline saline tobacco protein extract was then absorbed on an aluminum hydroxide gel adjuvant for purposes of enhancing its antigenicity. White male albino rabbits of the New Zealand strain each weighing approximately two and one-half kilograms were used for purposes of immunization. Each animal received a total of 31.5 mgm. of protein nitrogen through a series of nine intramuscular injections of the tobacco protein aluminum-hydroxide gel extract, each consisting of

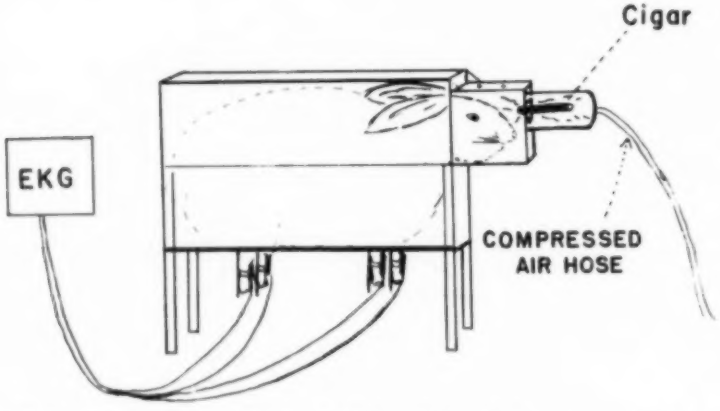

FIGURE 1: The simple "smoke-chamber" in which rabbits were exposed to a concentration of cigar tobacco smoke and subjected to forced inhalation of smoke-laden air.

3.5 mgm. protein nitrogen, over a three week period. On the fourth week or approximately five to seven days following the last sensitizing injection each rabbit was bled through the central artery of the ear and the serum tested for the presence of circulating antibodies against tobacco protein. The criteria used for the presence of sensitization and the development of circulating antibodies was the demonstration of a ring of precipitate at the interfacial point of contact of the tobacco protein extract layered upon the rabbit serum in a small serologic test tube.

Exposure to Tobacco Smoke: White, albino, male rabbits of the New Zealand strain of similar age, each weighing approximately two and one-half kilograms were used throughout these experiments. Series of both normal non-sensitized rabbits and those immunized with the tobacco protein extract were subjected to the forced inhalation of tobacco smoke in a specially constructed "smoke-chamber" (Figure 1), and to several other types of challenges. The smoke-chamber consisted of a simple wooden box in which the animals were held during the experiments. Four apertures on the floor of the box allowed for the protrusion of the front and hind legs; and the large hole in front of the chamber held the protruded head of the rabbit in place. A movable and smaller second chamber, hinged to the front of the box, was made to cover the extended head. The front wall of the smaller chamber was pierced by a tube-like holder, into which was placed a lighted cigar and which was covered by a tin can screwed to the box. At the opposite end of the tin can was an aperture into which was attached a piece of rubber tubing leading to a source of compressed air. By allowing the compressed air to pass through the cigar and through the holder, a stream of tobacco smoke was forced into the head chamber and thus the rabbit was subjected to the forced inhalation of the cigar smoke. Suitable apertures were placed in the roof of the head chamber allowing for the escape and evacuation of the tobacco-smoke-laden air in order to prevent suffocation of the animal. The concentration of the smoke was controlled by the rate of flow of the com-

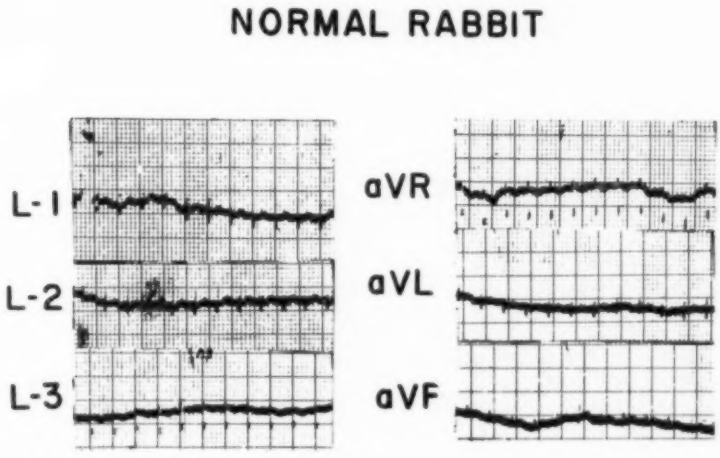

FIGURE 2: Six-lead electrocardiogram of a normal rabbit. Standardization at one and one-half millivolt. Rate is at about 300 per minute.

pressed air. Throughout the experiments the source of the tobacco was kept constant by using only one brand of cigar, and this was chosen because its tobacco leaf source was identical with that of the tobacco leaf in the preparation of the extract utilized for the immunization of the sensitized rabbits.

Recording of Electrocardiographic Tracings: Standard electrodes were attached to steel needles inserted into the skin of the shaved extremities of the rabbit protruding from the specially constructed wooden box (Figure 1). By means of standard methods and technics, electrocardiographic tracings were recorded of the standard limb leads 1, 2 or 3 on a direct writing electrocardiograph. In order to reduce to a minimum any interference that might be caused by leg motion these rabbits were lightly anesthetized with intravenous sodium pentobarbital. After a normal electrocardiographic tracing of the standard limb lead 2 was obtained, each rabbit was then subjected to the challenging experiment. The standard limb lead 2 was recorded throughout the entire experimental procedure until either the electrocardiographic pattern had returned to normal, was noted to become irreversible, or until all electrical activity in the heart had ceased. A series of normal non-sensitzied rabbits and another series immunized with a tobacco protein extract were subjected to the same experiments, and to similar challenges, during the process of which electrocardiographic tracings were recorded. The criterion for successful sensitization was the demonstration of circulating antibodies capable of precipitating tobacco protein *in vitro*. These challenges in cluded: (a) Forced inhalation of cigar smoke; (b) asphyxiation by mechanical suffocation; (c) respiratory depression by overdosage of intravenous nembutal; (d) intravenous injection of extract of tobacco protein. Table I illustrates the number of rabbits in both series subjected to the various challenging procedures. Althogether, a total of 14 normal rabbits and a total of 13 tobacco sensitized rabbits were subjected to various challenges. Four rabbits died of unrelated causes and under different circumstances and are not included in these series.

TABLE I

TABULATION OF GROUPS OF NORMAL AND TOBACCO-PROTEIN-SENSITIZED RABBITS SUBJECT TO VARIOUS CHALLENGING EXPERIMENTS

Nature of Challenge	Number of Normal Rabbits	Number of Tobacco Sensitized Rabbits
1. Forced inhalation of cigar smoke	8 (Series I)	6 (Series II)
2. Asphyxiation by suffocation	2 (Series III)	1 (Series VI)
3. Over dosage of Intravenous Nembutal	2 (Series V)	2 (Series VI)
4. i.v. injection of tobacco protein extract	2 (Series VIII)	4 (Series VII)

Results

Figure 2 represents the electrocardiogram of a normal rabbit. The heart rate is at about 300 per minute. All the complexes of a normal cycle are fairly clearly identified. The standardization is at one and one-half millivolts so that the amplitude of complexes is exaggerated by 50 per cent.

Series I.—Comprised eight normal non-sensitized rabbits used as controls subjected to the forced inhalation of cigar tobacco smoke. All of these eight animals developed abnormal electrocardiographic changes. These abnormalities, although not identical, appeared to be quite similar and fell into similar patterns so that they can be described as one pattern common to all the animals in the group. The earliest change noted was a sinus slowing of the heart rate (Figure 3). This was a most constant finding. The slowing appeared quite soon after the application of smoke; almost always within one to two minutes and occasionally within one-half minute. Soon after and within 10 to 15 minutes, depending upon the concentration of the smoke in the head chamber, other abnormalities appeared in the conduction system. The most common and prevalent were A-V conduction defects of various degrees which eventually terminated in ventricular asystole in every case. Almost always there were

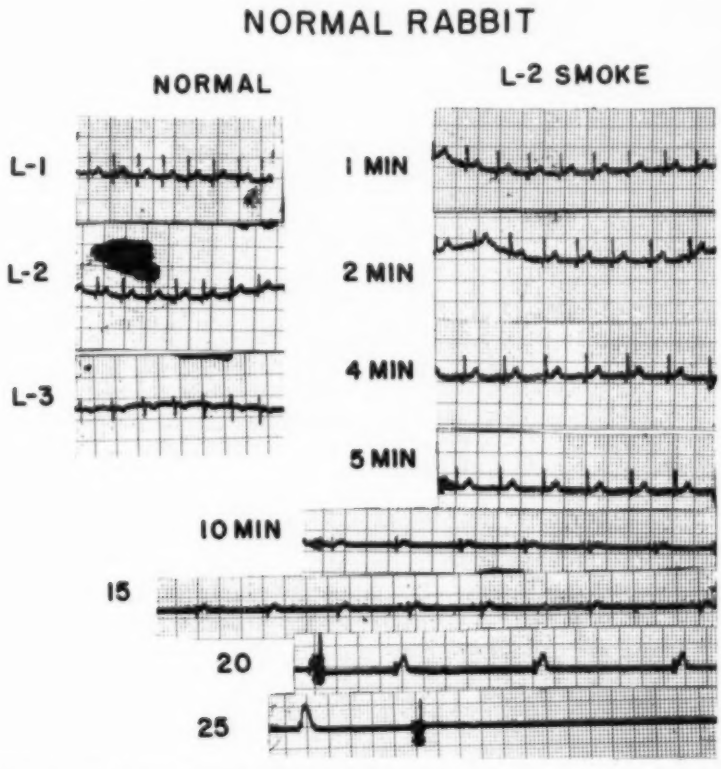

FIGURE 3: Electrocardiogram of a normal rabbit before and after exposure to forced inhalation of cigar tobacco smoke.

T-waves abnormalities. Early during the exposure there was noted a flattening of the T-waves but later other bizarre T-waves often developed. There were also changes in the amplitude of the QRS complex, and occasional bizarre arrhythmias. Figures 3 and 4 illustrate examples of these abnormal electrocardiograms. Introduction of air into the head chamber early during the challenging experiment often caused a reversal of the abnormal pattern. However, almost always the pattern became irreversible after the A-V block had become of sufficient severity. An example of this is illustrated in Figure 4. In most of these animals death usually occurred within 30 minutes but there were significant variations from animal to animal. Death always ensued with ventricular asystole.

Series II.—Comprised six rabbits sensitized to tobacco protein and subjected to the challenge of forced inhalation of cigar tobacco smoke. Here again, the predominant changes were: (1) A sinus slowing of the heart rate within a few minutes; (2) Irregularities of A-V conduction; (3) T-wave changes; (4) QRS changes of amplitude and shape; (5) Occasional tachycardias and (6) Eventual ventricular asystole. In comparison with those of Series I, although the patterns of tracings were not always identical, yet the predominant changes were alike; mainly, sinus slowing, A-V conduction irregularities and ventricular asystole. Figure 5 illustrates the tracing of one of these tobacco sensitized rabbits subjected to the forced inhalation of tobacco smoke. At the end of 30 minutes the rabbit died in ventricular asystole.

Series III.—Comprised two normal non-sensitized rabbits subjected to asphyxiation by mechanical suffocation, and,

Series IV.—One tobacco sensitized rabbit subjected to the same challenge of asphyxiation by suffocation.

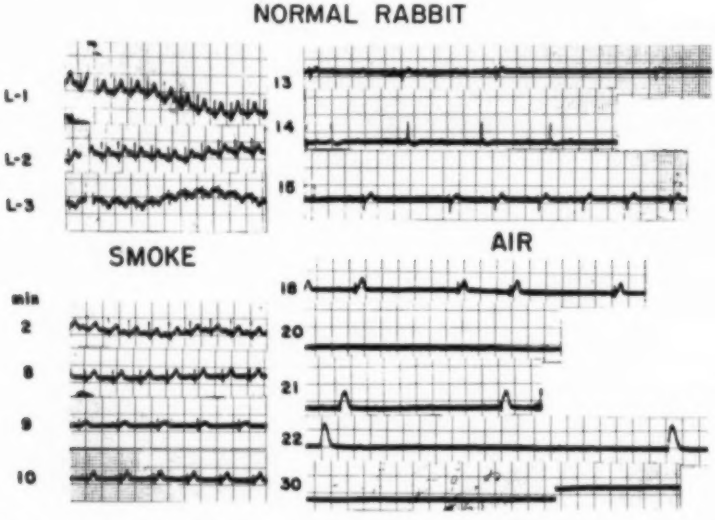

FIGURE 4: Electrocardiogram of a normal rabbit before and after exposure to forced inhalation of cigar tobacco smoke. At the end of 15 minutes of exposure, smoke is discontinued and free air is introduced into the chamber.

All of the three rabbits in series III and IV developed electro cardiographic abnormalities fundamentally similar in nature. Within a few seconds after the attempt at suffocation there developed an immediate sinus slowing followed by flattening of the T-waves and eventual A-V block and ventricular asystole. Irregular tachycardias developed inter mittently for short periods. All three rabbits died in ventricular asystole following A-V dissociation. Termination of the attempt at suffocation early during the experiment was followed by a reversal in the electrocardiographic pattern. However, the process became irreversible after the A-V block was well established. All three animals died within a few minutes. Figure 6 illustrates an example of the electrocardiogram of one of these three rabbits.

Series V.—Comprised two normal rabbits subjected to an overdosage of intravenous nembutal, and,

Series VI.—Two tobacco sensitized rabbits subjected to a similar overdosage of intravenous nembutal.

Figure 7 illustrates an example of the electrocardiogram of one of the two normal non-sensitized animals. The predominant changes were similar in the other two sensitized rabbits. Marked A-V dissociation and eventual ventricular asystole appear to be the main abnormal features in all the four rabbits.

Series VII.—Comprised a group of four tobacco sensitized rabbits subjected to the challenge of a large intravenous dose of extract of tobacco protein. Figure 8 illustrates an electrocardiographic example of response to this challenge. Immediately after the injection there is noted a marked slowing of the heart rate. However, within a few minutes the pattern reverses towards the normal and in seven minutes the tracing appears

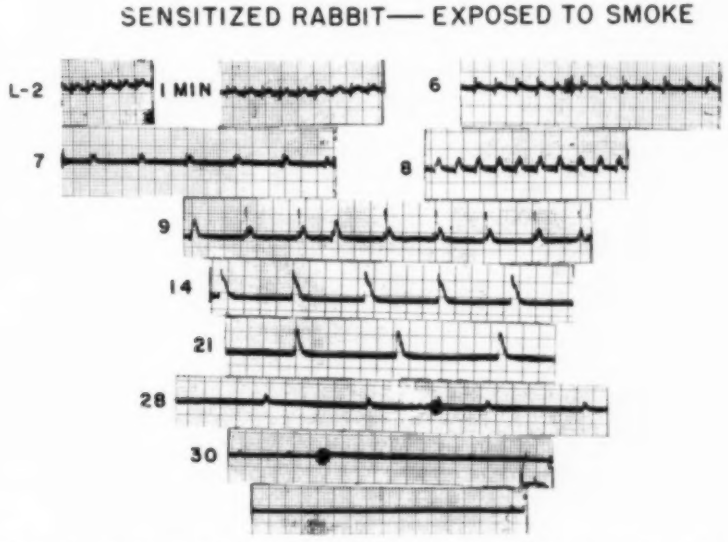

FIGURE 5: Electrocardiogram of a tobacco-protein sensitized rabbit before and after exposure to forced inhalation of cigar smoke.

to be similar to the original normal. A definite A-V block has not developed. The rabbit survived without evidence of anaphylactic shock. Figure 9 illustrates another example of the response to this same challenge. The effect of the intravenous injection of the extract does not appear to be outstanding on the electrocardiogram. A second injection following the first reveals no further significant effect.

Series VIII.—Comprised two normal non-sensitized rabbits subjected to similar injection of intravenous tobacco protein extract. Electrocardiograms of these rabbits revealed no significant change from these of Series VII, and were quite similar to pattern noted in Figures 8 and 9.

Discussion

The first difficulty encountered in the attempt to reproduce experimental sensitization to tobacco protein in rabbits was the finding that the tobacco protein extract was an extremely weak antigen. However, by the use of aluminum hydroxide gel as an adjuvant on which the tobacco protein was absorbed, the antigenicity was sufficiently enhanced so that the rabbits responded to these intramuscular injections with the production of detectable circulating antibodies. The criteria used for the presence of sensitization was the demonstration of precipitating antibodies against tobacco protein, as governed by standard serologic procedures. Only those animals with demonstrable precipitating antisera were included in the various "sensitized" series.

Throughout the experimental procedures tobacco leaves of only one source were consistently used for the purpose of producing both the tobacco-protein-extract for immunization and the tobacco-smoke for forced inhalation technics. This was felt to be specially important in view of the known variable qualitative and quantitative

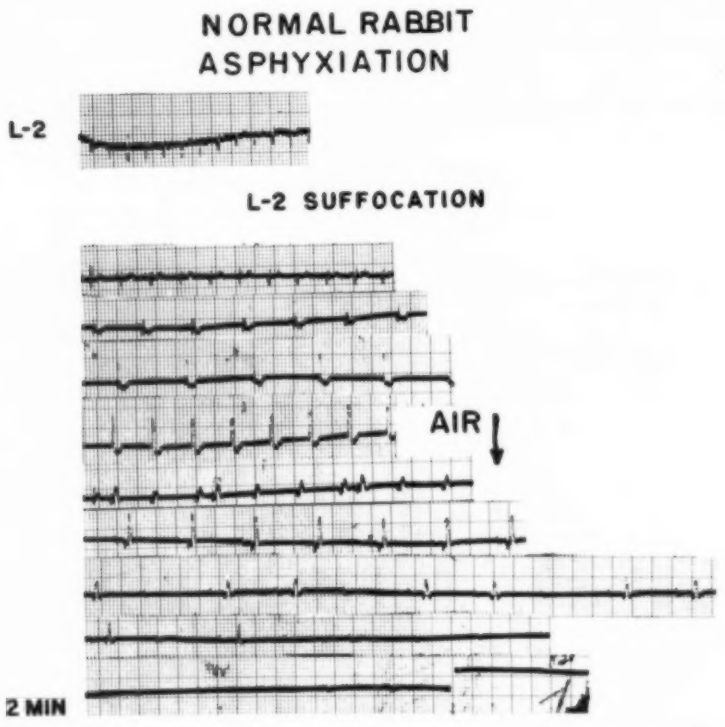

FIGURE 6: Electrocardiogram of a normal rabbit before and after subjection to mechanical suffocation. Midway during the experiment suffocation is terminated and the animal is exposed to free air.

protein content of tobacco leaves of different sources. It was felt that the use of cigar smoke would be preferable to cigaret smoke in that the smoke content of cigars would be entirely of a tobacco source devoid of the complicating factors present in cigaret paper-wrapper. Proteins initially present in the green tobacco leaves undergo a sharp decrease during the "curing" process due to the proteolytic enzymes naturally present in the tobacco leaves. The residual amount of protein in the finally cured leaves depends upon the type of tobacco used and the intensity of the curing process itself. We preferred to use the commercially available "cured" leaves rather than the green leaf because the smoke obtained from the former would most closely approximate that to which the average individual smoker is daily exposed.

For the purpose of obtaining satisfactory electrocardiographic tracings without somatic interference of movement, tremors, etc., it was necessary lightly to anesthetize the experimental animals with intravenous sodium pentobarbital. A possible influence of this drug on both anaphylactic responses and electrocardiographic patterns must be considered. Drinker and Bronfenbrenner[9] and Cohen and co-workers[10] suggest that anesthesia employed in their studies did not interfere with the production of anaphylactic shock in rabbits and Chase[11] is of the opinion that anesthetics are of low order in this regard. The studies of Cohen and co-workers[10] tend to rule out the possibility of anesthetics, of the type used here, effecting the electrocardiographic pattern of normal rabbits. Based on our preliminary studies in establishing the technics for these experiments, it is our opinion that this is probably true only within the range of the small dosage of anesthetic used by us in producing light anesthesia. However, as it was shown in Figure 7, both normal and tobacco-sensitized rabbits subjected to an overdosage of intravenous nembutal developed similar electrocardiographic abnormalities and did in ventricular asystole. We therefore suggest that a clear cut distinction should be made about the range and depth of anesthesia, at least as far as its effect on the electrocardiogram is concerned.

Reports on the effect of anaphylactic shock on the electrocardiogram of sensitized animals have failed to agree on any one pattern being typical of this state. Auer and Robinson[12] reported electrocardiographic disturbances in conduction ranging from slight delay to partial and complete heart block. Criep[13] noted the development of conduction disturbances progressing to cardiac standstill. Mikulicich[14] recording electrocardiograms in rabbits after intravenous challenge, did find ST segment and T-wave changes suggestig a pattern that might be attributed to involvment of the coronary vasculature.

It is interesting to note that in most of our "challenging experiments the electrocardiographic abnormalities observed were fairly consistent from one series to the other with the exception of the two groups receiving intravenous tobacco-protein extract. These abnormalities appeared to fall into six major groups: (1) Sinus slowing; (3) Various degrees of A-V conduction defects and A-V dissociation; (3) Bizarre arrhythmias; (4) T-wave changes which did not appear to be very prominent; (5)

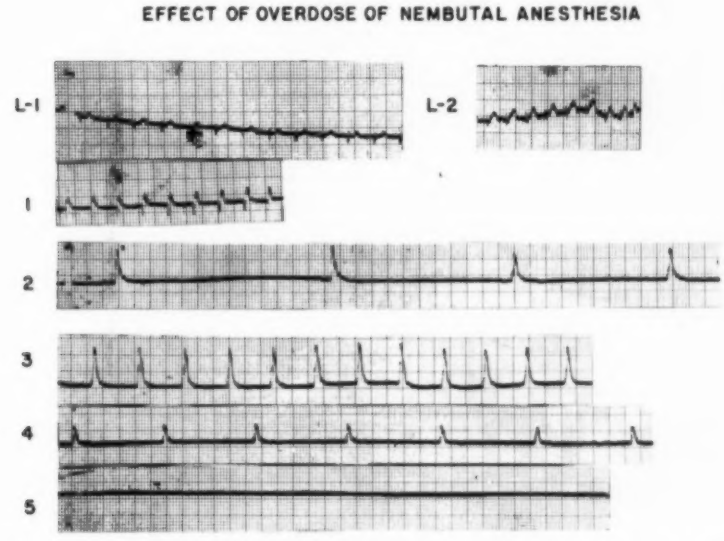

FIGURE 7: Electrocardiogram of a normal rabbit before and after subjection to overdosage of intravenous nembutal anesthesia.

Changes in the amplitude of the QRS complex; and (6) Ventricular asystole. The most consistent abnormality appeared to be a slowing of the ventricular rate, at least partly due to various degrees of A-V block and dissociation. In all instances of death, the end result was heralded by ventricular asystole followed by auricular and then complete cardiac standstill. Arrhythmias were less common. Many T-wave abnormalities were noted but these did not constitute the dominant pattern. Some of the T-wave abnormalities suggested hyperpotassemic patterns. Even more interesting is the consistent observation in our experiments that the abnormal electrocardiographic patterns are generally similar in both the tobacco-sensitized and the non-sensitized groups of rabbits subjected to the various challenges; and that these abnormal patterns in one series do not differ significantly from the abnormal patterns noted in other series, with the exception of the two series in which the animals were subjected to intravenous injections of tobacco protein extract. In other words, the abnormal electrocardiographic patterns are quite alike in both the sensitized and the non-sensitized groups of rabbits subjected to forced inhalation of tobacco smoke, to asphyxiation, and to intravenous nembutal overdosage. Death of the animals was the ultimate result for all the rabbits subjected to these three challenges. On the contrary, the rabbits subjected to injections of tobacco protein extract not only did survive but even failed to develop the electrocardiographic abnormalities noted in the animals of the other series. It is noteworthy that the severe challnge of the intravenous injection of the tobacco protein extract failed to elicit any manifestation of anaphylaxis even in the animals previously sensitized to tobacco protein; and that no significant difference was noted with this challenge between the sensitized and the non-sensitized groups. These facts pose several serious questions: first, whether or not these animals were made truly sensitive to the tobacco protein, and second, if they were, how could one explain the absence of anaphylaxis as a response to exposure to a large intravenous dose of the antigen, the tobacco-protein-extract. If we have to accept the basic mechanism of death and the electrocardiographic abnormalities in the rabbits exposed to tobacco-smoke, to be due to an antigen-antibody reaction, then the animals most susceptible to this type of a mechanism should have been those subjected to the tobacco extract itself most directly by the intravenous route. The negative results in this series throw some doubt upon the existence of

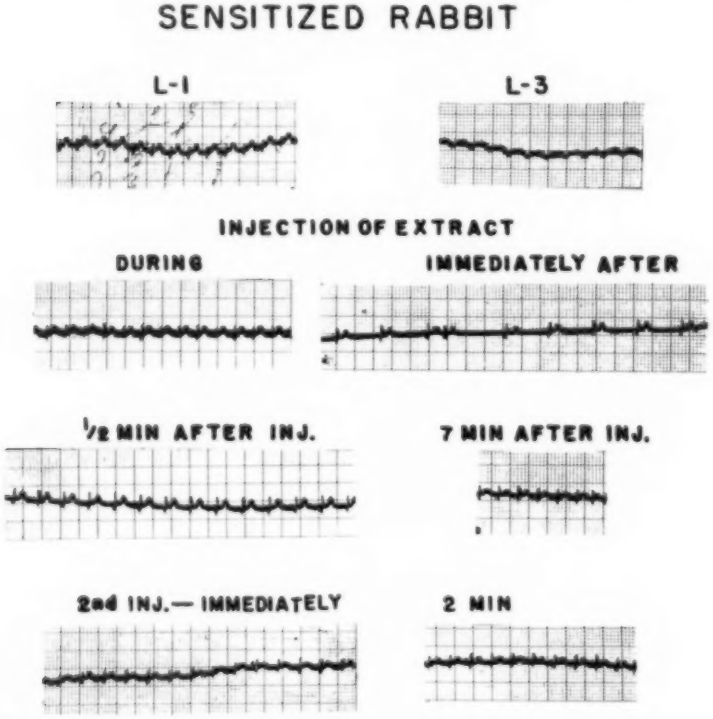

FIGURE 8: Electrocardiogram of a tobacco sensitized rabbit before and after intravenous injections of tobacco protein extract.

true hypersensitivity to tobacco protein. An analysis of the facts in the case of the animals subjected to the other three types of challenges, that is, exposure to tobacco-smoke, suffocation and nembutal overdosage, suggests that the mechanism, the common denominator in the production of these abnormal effects, is probably *one and the same* for all. We are inclined to feel that this factor is *anoxia*: anoxia, caused by a concentration of the smoke in the head chamber; anoxia, caused by suffocation; and anoxia, caused by respiratory depression in the case of nembutal overdosage. Further evidence is afforded along this line by the failure of the intravenous injection of the tobacco extract itself to produce similar electrocardiographic abnormalities as those produced by the other challenges. These facts in general fail to support the possibility of an antigen-antibody type of reaction to be the basic mechanism in the production of these abnormalities described above.

In this regard it is specially important to note the studies reported by Criep[13] in which identical cardiac changes, especially those of conduction defects and complete heart block, were recorded in the rabbit during experimentally induced procedures of anaphylaxis, asphyxia, and mechanical clamping of the pulmonary artery. Criep had indicated that these cardiac changes observed were probably due to myocardial anoxemia and possibly cerebral anoxemia occurring during the state of asphyxia secondary to anaphylaxis.

While it is entirely possible that prior sensitization to tobacco protein does influence cardiovascular responses to inhalation of tobacco smoke, the finding of similar changes in both the tobacco-sensitized and the non-sensitized animals would suggest

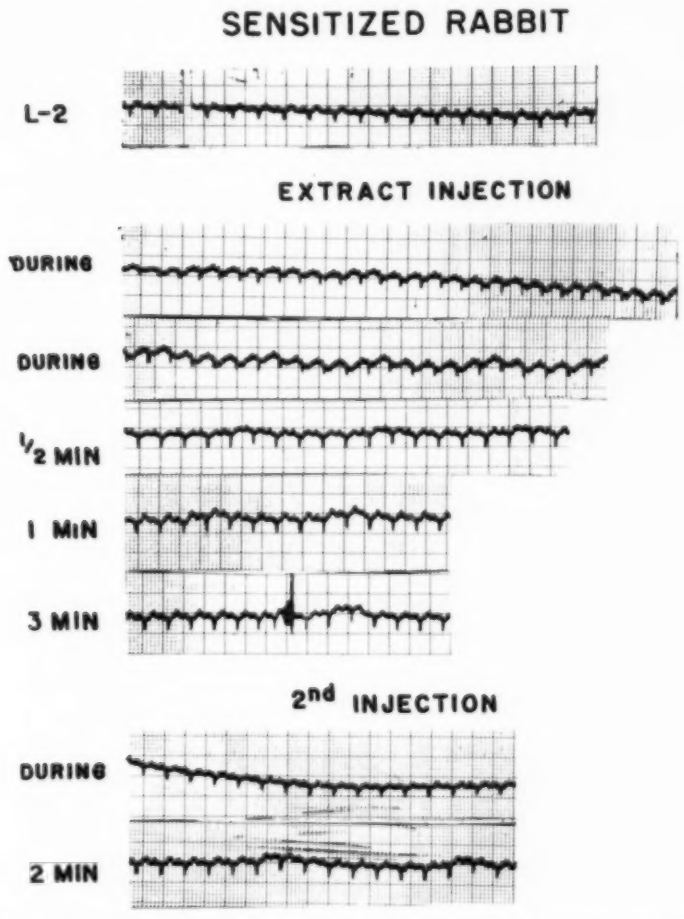

FIGURE 9: Electrocardiogram of a tobacco sensitized rabbit before and after two separate intravenous injections of tobacco protein extract.

that a common mechanism does exist in both groups. Even at the risk of repetition, the probability of asphyxia to be this common factor must be stressed. Other reasons for this assertion again are based upon the finding of similar electrocardiographic changes in previously normal rabbits subjected to suffocation procedures, as well as in rabbits during asphyxia experiments.[13, 14] In this regard it is important to point out that appreciable amounts of carbon monoxide may be present in tobacco smoke with that of cigar smoke yielding up to 6 per cent of this noxious gas by volume.[16] In this manner, 5 to 10 per cent of circulating hemoglobin may be converted to carboxyhemoglobin following smoking,[16] and thus it is entirely possible that this may have been a factor in the irreversible changes noted on the electrocardiograms. The effect of the nicotine content of the tobacco smoke must also be considered. However, Bellet and co-workers[15] found that this exerted only a slight effect on normal dogs, whereas in the presence of acute myocardial damage produced by coronary ligation, there was an increased sensitivity to nicotine. It is also quite important to note here that in addition to the protein and nicotine content, tobacco as commercially available, contains a variety of other substances. These include alkaloids other than nicotine, such as nornicotine and myosmine, aldehydes, ketones, volatile acids, phenols, pyridine and other nitrogenous bases, hydrocarbons, and a variety of additives including glycerol, triethylene and diethylene glycols. Unfortunately, most commercial "denicotinized" tobaccos still contain significantly large amounts of the alkaloids[16] that would interfere with its proper evaluation in a study of this type.

Further studies along these lines including the attempt to produce a more highly refined tobacco protein extract containing lesser amounts of nicotine and other pharmacologically active constituents is a matter for further investigation.

SUMMARY

(1) Within the limits of these experiments it can only be stated that prior sensitization to tobacco protein does not appear to influence to any significant degree the cardiovascular response of rabbits to these various challenging situations, such as, forced tobacco smoke inhalation, asphyxiation, respiratory depression and exposure to tobacco protein extract.

(2) Anoxia, mediated through various channels, such as asphyxiation, respiratory depression, etc., appears to be the basic mechanism responsible for the death of the animals and for the electrocardiographic abnormalities in these experiments.

(3) These cardiovascular effecas demonstrated by abnormalities of the electrocardiogram: (a) probably are not due to any anaphylaxis; (b) probably do not represent in immunologic reaction of hypersensitivity; and (c) probably are not due to the pharmacologic effects of nicotine.

(4) In the rabbit, the mechanism of death due to anoxia, appears to be mediated by the development of various types and degrees of A-V bloc, A-V dissociation, sinus block, and eventual ventricular asystole.

Acknowledgment: We wish to express our thanks to Mr. Stanley Yancis, and to Miss Eugenie Mundy of the Medical Service, for their invaluable technical assistance during the animal experiments. We also wish to thank Mr. William D. Bohon, Chief Medical Illustrator, Veterans Hospital, New Orleans for his efforts in producing the illustrations.

RESUMEN

1. Según la limitada experiencia aquí relatada, sólo puede declararse que la sensibilización previa a la proteina del tabaco no parece influir en grado significante la respuesta cardiovascular de los conejos en varias situaciones de provocación como la inhalación forzada del humo de tabaco, asfixia, depresión respiratoria y exposición del extracto de proteina del tabaco.

2. La anoxia obtenida por varios medios como asfixia, depresión respiratoria, etc., parece ser el mecanismo básico responsable de la muerte de los animales y de las anormalidades electrocardiográficas en estos experimentos.

3. Estos efectos electrocardiográficos: (a) no son debidos probablemente a ninguna clase de anafilaxia; (b) probablemente no representan una reacción inmunobiológica de hipersensibilidad; (c) probablemente no se deben afectos farmacológicos de la nicotina.

4. En el conejo, el mecanismo de la muerte debida a anoxia, parece ser producido por varios tipos y grados de bloqueo de A-V, disociación de A-V, bloqueo sinusal, y eventual asístole ventricular.

RESUME

1. Dans les limites de l'expérimentation, on peut constater que la sensibilisation antérieure à la protéine du tabac ne semble pas influencer de façon appréciable la réaction cardiovasculaire des lapins soumis à différentes situations particulières telles que l'inhalation forcée de fumée de tabac, l'asphyxie, la dépression respiratoire et l'exposition à l'extrait protéinique de tabac.

2. Dans ces expériences, l'anoxie, provoquée par différents procédés, tels que l'asphyxie, la dépression respiratoire, etc., semble être le mécanisme fondamental responsable de la mort des animaux, et des anomalies électrocardiographiques.

3. Ces effects cardiovasculaires, mis en évidence par les anomalies de l'électrocardiogramme:

a) ne sont probablement pas dûs à une anaphylaxie;

b) ne reprèsentent probablement pas une réaction immunologique d'hypersensibilité;

c) ne sont probablement pas dûs aux effets pharmacologiques de la nicotine.

4. Chez le lapin, le mécanisme de la mort due à l'anoxie, semble être amené par le développement de différents types et degrés de block auriculo-ventriculaire, de dissociation auriculo-ventriculaire, de bloc sinusal et éventuellement d'asystole ventriculaire.

ZUSAMMENFASSUNG

1. Innerhalb der Grenzen dieser Experimente kann nur festgestellt werden, dass vorausgehende Sensibilisierung auf Tabak-Proteine nicht in irgendwelchem signifikanten Grad die cardiovasculäre Reaktion von Kaninchen zu beeinflussen scheint gegenüber solchen verschiedenartigen Belastungsproben wie forcierte Tabakrauch-Inhalation, Erstickung, Herabsetzung der Atmung und Exposition auf Extrakt von Tabak-Proteinen.

2. Anoxie, wie sie auf verschiedenen Wegen vermittelt wird, so duch Asphyxie, Herabsetzung der Atmung usw., scheint der grundlegende Mechanismus zu sein, der verantwortlich ist für den Tod der Tiere und für die elektrokardiographischen Veränderungen in dieser Experimenten.

3. Diese durch Veränderungen im EKG nachgewiesenen kardiovasculären Wirkungen sind (a) wahrscheinlich nicht die Folge irgendwelcher Anaphylaxie; (b) stellen wahrscheinlich keine immologischen Überempfindlichkeits-Reaktionen dar; und sind (c) wahrscheinlich nicht die Folge der pharmakologischen Nikotin-Wirkungen.

4. Beim Kaninchen scheint die tödliche Wirkung infolge Anoxie vermittelt zu werden durch die Entwicklung verschiedener Typen und Grade eines A-V-Blocks, einer A-V-Dissoziation, Sinusblock und ev. Kammer-Asystolie.

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The Modifications of the Electrocardiogram in Chronic Pulmonary Tuberculosis

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The Method

We wish to report on the results of systematic research carried out for a period of over seven years in some 8,000 patients having chronic unilateral or bilateral pulmonary tuberculosis. Some were subjected to surgical treatment including extrapleurical A.P. thoracoplasties, partial or total resections, and decortication.

The greater part of the tracings have been frequently repeated, and especially on the occasion of spontaneous modifications or those provoked by treatment, medical or surgical, appearing in the pulmonary picture.

The electrocardiographic observations have been carried out making use of all the derivations of Einthoven (D1, D2, D3) unipolar of the limbs according to Goldberger (aVR, aVL, aVF) and unipolar-precordial according to Wilson (from V1 to V6).

Since some localized lesions are recorded only in a few and particular derivations, barring the effective selectivity of each derivation for the single and partial electric effects which take place in a myocardic sector, we have added the thorax derivations of Condorelli and the right side thorax derivations of Di Maria to the recording of the normal standardised derivations (Figure 1 shows the normal morphology).

The tracings have been kept sufficiently long because several peculiar recordings might appear sporadically or be quite inconstant.

The study of the same tracings under examination, has been carried out considering also separately the alterations which could be attributed to the damage of the specific myocardium and those which could be referred to the contractile myocardium, and the possible alterations of the pericardium as well.

Statistical Results

If we examine the single alterations of the electrocardiogram from a strictly statistical point of view, we may get the following results:

1) The electrocardiographic investigation of 8,000 cases has ascertained in 2,850 cases, equal to 35.62 per cent, the existence of alterations in at least one of the tracings.

2) The alterations of the electroatriogram (morphological alterations of voltage, P of the pulmonary type, P negative in D2 and D3, lengthening and shortening of the section P-Q and level changes of the same section) have been found in 103 cases, equal to 12.76 per cent, if referred to all of the examined cases combined, and equal to 35.94 per cent if referred to the cases with abnormal modifications of the electrocardiogram.

3) Alterations of the electroventriclegram (morphological alterations and atypical of the QRS, so called heart nerve blockage, syndrome of W.P.W. and alterations of section ST and T) have been documented in 1010 cases, equal to 12,625 per cent if referred to all of the studied cases

TABLE I—ALTERATIONS OF THE ELECTROATRIOGRAM

Type of alterations	Absolute number	Percentage on the total of cases (8,000)	Percentage of pathological cases per cent) (2,850 = 35.62
Morphological alterations and atypical alterations of voltage	675	8.43	23.68
P of pulmonary type	111	1.38	3.89
P negative in D2-D3	25	0.38	0.87
Lengthening of sections P-Q	160	2	5.40
Shortening of section P-Q	40	0.50	1.40
Level changes section P-Q	20	0.25	0.70
Total of alterations of the EAG	1,031	12.76	35.94

combined together, and to 35.85 per cent if referred to the cases with abnormal modifications of the electrocardiogram (Table II).

4) Alterations of rhythm (tachycardia and sinusal arrhythmia, paroxysmal-tachycardia, atrial and ventricular extrasystoles, flutter and atrial fibrillations) have been ascertained in 605 cases, equal to 7.625 per cent if referred to the total of subjects, and equal to 22.474 per cent if referred to cases with abnormal tracings (Table III).

5) Particular syndromes (myocardic lability, types S1-S2-S3, heart infarcts) have been found in 203 cases, with percentages of 2.54 per cent and 6.90 per cent (Table IV).

6) In 9.75 per cent of cases deviations have been observed to the right side of the electrical axis and in 5 per cent with deviations on the left side.

There are therefore pictures particular and different, sometimes combined, sometimes in succession, and often isolated.

These can be classified as syndromes from the depression of the excit-

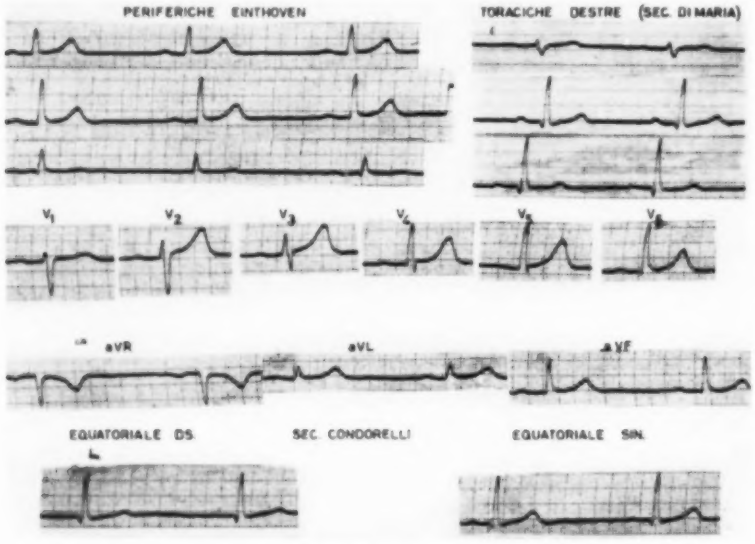

FIGURE 1: Normal traces of the derivations used in our EKG investigation.

TABLE II—ALTERATIONS OF THE ELECTROVENTRICLEGRAM

Type of alterations	Absolute number	Percentage on the total of cases (8,000)	Percentage of pathological cases (2,850 = 35.62 per cent)
Morphological alterations and atypical alterations of the QRS	200	2.50	7
So called heart nerve block	40	0.50	1.40
Syndromes of the W.P.W.	10	0.125	0.35
Alterations section S-T and T	760	9.50	27.10
Total of alterations of the EVG	1010	12.625	39.85

ability, attributable to sinus deficiencies, to disturbances of the sinus-atrial and in part intraventricular conducibility, and syndromes from the increase of the excitability of the specific myocardium.

More frequently have been observed the respiratory arrhythmia, and the deformation of the atrial morphology which can appear also sporadically without being accompanied by alterations of the rhythm.

The sinus arrhythmia has been almost always observed in association with those electrocardiographic pictures which Di Maria has defined myocardic lability.

Such pictures are characterized by the existence in the same tracing, besides the respiratory arrhythmia, by three phases of the QRS in D2 and D3, with modifications of voltage of the P and possible modifications of PQ time.

Frequently also the damage of the ways designed for the intraventricular transmission of the excitement has appeared and consequently the damage of the contractile myocardium depolarization ways.

But all these electrocardiographic abnormalities are not in any way specific and are similar to those observed during the course of rheumatic fever or other infectious diseases.

Among the syndromes due to the increase of the excitability of specific myocardium, the extrasistoles of either atrial or ventricular origin are noteworthy for their high frequency: however it does not seem that they can be linked with special myocardic conditions connected with a noticeable damage, and certainly their frequency is markedly superior to that which has been ascertained because they have been found only partially

TABLE III—ALTERATIONS OF RHYTHM

Type of alterations	Absolute number	Percentage on the total of cases (8,000)	Percentage of pathological cases (2,850 = 35.62 per cent)
Sinus tachycardia	160	2	5.40
Sinus arrhythmia	360	4.50	12.20
Atrial and ventricular extrasistoles	80	1	2.70
Flutter and fibrillation	3	0.037	0.105
Paroxysmal tachycardia	2	0.025	0.070
Total of alterations	605	7.562	22.475

TABLE IV—PARTICULAR SYNDROMES

Type of alterations	Absolute number	Percentage on the total of cases (8,000)	Percentage of pathological cases (2,850 = 35.62 per cent)
Myocardic liability	80	1	2.70
Pictures of type S1-S2-S3	120	1.50	4.10
Heart infarct	3	0.037	0.105
Total of particular syndromes	203	2.54	6.905

in an electrocardiographic recording, which is, out of necessity, discontinous and sporadic.

Very rare are the atrial tachycardia and the paroxysmal tachycardia; only two cases of atrial fibrillation have been found.

In the field of electrocardiographic modifications, because of the contractile myocardium damage, the duration of the electric sistole has not presented noticeable modifications in the majority of cases, and the few variations which have been observed do not permit particular evaluations.

The picture which frequently emerges in the observation of our tracings, is the one which can be called "atrial or ventricular myocardic sufferance."

This picture refers to the morphological alterations and voltage alterations of the wave P and of the QRS and of the section S-T alterations and of the T which in our casuistics only emerges respectively as the 8.43 per cent, the 2.50 per cent and the 9.50 per cent.

These pictures have been termed "sufferance" instead of "myocardic damage" because quite frequently they have appeared as reversible damages or damages connected to the proximate period shortly after surgery on the thorax.

To these pictures can be associated the so called "myocardic lability" pictures according to Di Maria, which we have already mentioned.

These sufferance represents the biological consequence of the alterations and negative interferences brought on by the "anoxemia-toxemia" components in the field of the enzyme activities and of the physical-chemical changes which start and control the freeing of energy from the substrata and its adequate use for the nutrition and activity of the myocardic fibre.

SUMMARY

This preliminary paper contains general observations on the modifications of the electrocardiogram cases of chronic pulmonary tuberculosis.

1) The study has been continued for more than seven years on 8.000 patients. The tracings have often been repeated at intervals and have been recorded, besides the usual standard derivations like the peripheral ones according to Einthoven, the unipolar derivations of the limbs, and the unipolar precordial ones according to Wilson, also with the thoracic derivations of Condorelli and the right hand side thoracic derivations long since proposed by Di Maria.

2) The electrocardiographic research has revealed how of these 8.000 cases at least 2.850 (35,68 per cent), presented alterations in at least one of the tracings, and has allowed the division of their pathological aspects in three main groups selected with a clinical functional intent. It has not been possible to make evident an electrocardiographic pathognomonic picture for chronic pulmonary tuberculosis.

3) The multiplicity of the electrocardiographic pictures is justified by the fact that the factors generating the lesions of the cardio-vascular system in the course of the tuberculous affection, are different. The most important ones among these are represented by toxemia, anoxemia, the possible medical or surgical treatments, and the alteration of the electrolytic and immuno-biological constants of the organism.

Notes on the Condorelli and Di Maria methods

The precordial derivations, called "right side thorax derivations" by Di Maria, are obtained in the following way: the first, putting on the right hand margin of the second section, one electrode attached to the lead normally used for the right arm, and on the IV section, always on the same line, a second electrode attached to the lead of the left arm (commutator in D1); the second, putting on the second section the electrode attached to a lead of the right arm and on the left leg the lead normally reserved to this limb (commutator in D2); the third, putting the electrode of the left arm on the right margin of the IV section and leaving the one of the left leg on the original spot (commutator in D3).

The regulating is made with the usual voltage of 1 cm = 1 mV.

The derivations according to Condorelli, which are called "equatorial derivations," are two: 1) the right side equatorial derivation in which the electrode of the left arm is put on the section of the right median axillary line, and the electrode of the right arm on the left sub-clavicular region; 2) the left side equatorial derivation, in which the electrode of the right arm is put on the right sub-clavicular region and the electrode of the left arm is put on the left median axillary line on the VIII section.

RESUMEN

Esta comunicación preliminar contiene las observaciones generales de modificaciones del electrocardiograma en tuberculosis pulmonar.

1. Se ha hecho un estudio continuado durante más de siete años en 8,000 enfermos. Los trazos se han repetido con frecuencia y se han registrado además de las habituales derivaciones como las periféricas de acuerdo con Einthoven, las derivaciones unipolares de las extremidades y las precordiales unipolares de acuerdo con Wilson y también las desviaciones torácicas de Condorelli y las derivaciones del lado derecho hace mucho tiempo propuestas por Di Maria.

2. La investigación electrocardiográfica ha revelado como de estos 8,000 casos por lo menos 2,850 (35.68 por ciento) presentaron alteraciones cuando menos en uno de los trazos y esto ha permitido la división de sus aspectos patológicos en tres grupos principales seleccionados con propósitos clínicos funcionales.

No ha sido posible evidenciar un cuadro electrocardiográfico patognomónico de la tuberculosis pulmonar crónica.

3. La multiplicidad de los cuadros electrocardiográficos se justifican porque los factores que generan las lesiones en el aparato cardiovascular en el curso de la afección tuberculosa, son diferentes.

Los más importantes entre ellos están representados por la toxemia, anoxemia, los posibles tratamientos médicos y quirúrgicos y las alteraciones de las constantes electrolíticas e inmunobiológicas del organismo.

RESUME

Ce rapport préliminaire contient des observations générales sur les modifications électrocardiographiques que l'on peut noter dans la tuberculose pulmonaire chronique.

1. L'étude a été poursuivie pendant plus de 7 ans sur 8.000 malades. Les tracés ont souvent été répétés à intervalles réguliers, et, outre les dérivations standard habituelles telles que les dérivations périphériques selon Einthoven, les dérivations unipolaires des membres, les dérivations unipolaires précordiales, selon Wilson, ainsi que les dérivations thoraciques de Condorelli, et les dérivations thoraciques du côté droit depuis longtemps proposé par Di Maria ont été également enregistrées.

2. La recherche électrocardiographique a révélé comment, sur 8.000 cas, 2.850 au moins (35,78%) présentaient des altérations dans l'un des tracés au minimum. Leurs aspects pathologiques se divisent en trois groupes principaux, différenciés dans un but fonctionnel clinique. Il n'a pas été possible de mettre en évidence un type électrocardiographique pathognomonique de la tuberculose pulmonaire chronique.

3. La multiplicité des aspects électrocardiographiques est justifiée par le fait que les facteurs générateurs des lésions du système cardiovasculaire sont différents dans l'évolution de l'affection tuberculeuse. Les plus importants parmi ceux-ci sont représentés par la toxémie, l'anoxémie, éventuellement les traitements médicaux et chirugicaux, et l'altération des constantes électrolytiques et immuno-biologiques de l'organisme.

ZUSAMMENFASSUNG

Diese vorläufige Arbeit enthält allgemeine Beobachtungen über die Modifikationen des Elektrokardiogramms bei Fällen von chronischer Lungentuberkulose.

1. Die Untersuchung erstreckte sich über mehr als 7 Jahre und 8 000 Patienten. Die Kurven wurden oft in gewissen Zeitabständen wiederholt. Es wurde aufgezeichnet neben den gewöhnlichen Standardableitungen wie denen der Peripherie nach Einthoven die unipolaren Extremitäten-Abteilungen und die unipolaren praecardialen nach Wilson auch mit den Thoraxableitungen von Condorelli und den "rechte-Hand-Thorax-Seiten"-Ableitungen wie sie vor langer Zeit von Di Maria vorgeschlagen sind.

2. Die elektrokardiographische Forschung hat ergeben, dass von diesen 8 000 Fällen mindestens 2 850 (35,68%) Abweichungen in wenigstens einer der Ableitungen aufwiesen und ermöglichte die Aufteilung dieser pathologischen Befunde in 3 Haupt-

gruppen, die im Hinblick auf die klinische Funktion ausgewählt wurden. Es war nicht möglich, ein elektrokardiographisch pathognomonische Bild zu entwickeln, für chronische Lungentuberkulose.

3. Die Vielfalt der elektrokardiographischen Bilder ist gerechtfertigt aus der Tatsache, dass die Faktoren, die die Veränderungen des kardiovasculären Systems im Verlauf der tuberkulösen Affektion erzeugen, voneinander abweichen. Die wichtigsten unter ihnen stellen sich dar als Hypoxaemie, Anoxaemie, die möglichen internen oder chirurgischen Behandlungen und die Veränderungen der elektrolytischen und immunbiologischen Konstanten des Organismus.

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Trace Metals in Human Cardiac Physiology and Pathology

The importance of trace metals lies in their unique role in the activation of enzymes and enzyme systems, and in their interactions with the vitamins and the hormones. An enzyme is a protein, differing from other proteins only in its ability to catalyze profound metabolic reactions within the tissues. Metals enter into these reactions in either of two ways: (1) the enzyme itself may contain a metal as an indispensable part of the molecule, or (2) at times the metal is not an integral part of the enzyme molecule but merely interacts with the enzyme in catalysis. Often an enzyme is empowered to bring about either of two reactions: the presence of a metal which can be utilized as part of the enzyme system may then be a deciding factor, determining which of alternative reactions will occur. In some cases the reaction is specific and only a certain metal or metalloid can be utilized as a part of the enzyme system; for other enzyme systems, almost any bivalent metal will suffice.

Interrelationships between the trace metals are extremely complex and may be likened to a group of rings—each interconnected with every other ring by a series of rubber bands. Movement of any of the rings influences every other and may even cause reversal of the direction of an occasional ring. For example, copper deficiency in cattle may be due either to low copper concentration of pasture grasses or to their high molybdenum content, the degree of copper suppression by the molybdenum depending not only on the absolute amounts of copper and molybdenum present or on the copper-molybdenum ratio but also on the amount of inorganic sulfate in the diet, the amount of manganese available, and the amount of protein present. If the diet is very high in protein, manganese may augment rather than block the effects of molybdenum and sulfur on copper utilization.

In addition to their importance in enzymatic activity, certain of the metals also enter into or influence hormone and vitamin action and, reciprocally, metal content of the tissues is influenced by the hormones and by the presence of quantities of vitamins. The effectiveness of metals in such minute quantities, their interaction with enzymes and hormones, and the profound metabolic changes resulting from deficiency, toxicity or imbalance of trace metals—these all suggest an analogy to the vitamins.

Metals are intimately involved in fatty acid metabolism. Manganese, long recognized as a lipotrophic agent, increases cholesterol synthesis by 125 per cent; vanadium decreases synthesis by 90 per cent. In rats, Curran has shown that chromium increases by 150 per cent the incorporation of C^{14}-labeled acetate into cholesterol and fatty acids. The introduction of 8-hydroxyquinoline decreases cholesterol and fatty acid synthesis, suggesting that various metals are mobilized or removed by the metal-binding agent. When we subjected cardiac tissues obtained at necropsy to spectrographic and microchemical analysis, we found that manganese levels were markedly reduced in areas of fresh myocardial infarction.

Copper metabolism is concerned in protein metabolism. Total serum copper level is elevated roughly 141 mcg/100 ml. in portal Laennec's cirrhosis; biopsy specimens disclose that early deposition of excess copper *precedes* clinical evidence of cirrhosis. On the other hand, hypocupremia accompanies the hypoalbuminemia and hypogammaglobulinemia sometimes observed in infants on a milk diet, and may be noted during relapse in patients with sprue. This hypocupremia has been attributed primarily to an inability to synthesize ceruloplasmin. Ceruloplasmin is important and significant in the diagnosis of schizophrenia, wherein administration of ceruloplasmin has induced complete remission in nine out of ten otherwise untreated patients. Apparently, ceruloplasmin has a protective action, cushioning the organism against stress. This protective aspect of ceruloplasmin is unrelated to the adrenal gland.

Schroeder and Perry have pioneered in elucidating the roles of the trace metals in arterial hypertension. After the discovery that hydralazine, an antihypertensive agent, selectively binds manganese, ferrous iron, copper, silver, tin and mercury, and that hydralazine is oxidized with the liberation of nitrogen by vanadium and ferric iron, these investigators tested a number of chelating and metal-binding agents and found that several will lower arterial hypertension. They found that many apparently dissimilar substances—none of which acts on the autonomic nerves—possess the common property of binding trace metals. Cadmium, lead and manganese are found in increased amounts in the blood serum and in the urine of patients with malignant hypertension. When hypertensive patients are treated with agents such as hydralazine, high urinary levels of these metals drop toward normal. Excretion of one metal, vanadium, is considerably less in hypertensive patients than in normal persons. Determination of the roles of metalloenzyme imbalance in arterial hypertension and the correct apportionment of the contribution of each trace metal to that imbalance must wait on the thorough study of a large series of cases.

We are learning more and more about the roles of ions other than sodium in the pathogenesis and control of congestive failure. Cadmium, one of the metals implicated in arterial hypertension, also is intimately concerned in congestive heart failure, wherein excess cadmium is believed to have a dampening effect on amplitude of the contraction of cardiac tissue. Less well known is the method of action of carbonic anhydrase inhibitors. Here, too, a metal is of primary importance, for carbonic anhydrase inhibitors work by blocking the action of zinc, the metal which is an indispensable part of the carbonic anhydrase molecule. Removal of the zinc results in irreversible inactivation of the metalloenzyme; reversible inactivation is effected by enzyme inhibitors which combine with zinc, such as dimercaprol, cyanide, sulfide, azide and the sulfonamides. A third metal, mercury, commonly is administered in the treatment of congestive failure. In the clinics conducted at the Los Angeles County Hospital, we have maintained patients free from significant renal disease for months or years on moderate or massive doses of organomercurials without injury to kidney function, provided neither oliguria nor hyponatremia was present. Analysis of kidney tissue from 45 patients with congestive failure showed an increase of mercury deposit in the kidney with continued administration but gave no evidence of interference with kidney function. Non-

protein-nitrogen values for these patients cannot be interpreted as indicating that the larger amounts of mercury in the tissues were harmful.

Zinc, which determines the rate of release of insulin from the beta cells of the pancreas, is very low in the diabetic heart—especially in the left ventricle. As zinc values in the liver are not lowered, we feel that the low concentrations of zinc in the heart may well reflect the diabetic state.

For at least one metal, cobalt, method of administration may be of some significance, as the oral administration of cobaltous chloride to cholesterol-fed rabbits and chickens has been shown to reduce the incidence and severity of aortic atheromatous lesions and to lower blood cholesterol concentrations. On the other hand, parenterally-administered cobalt increases the incidence and severity of aortic lesions and raises the level of cholesterol in the blood. This finding has important implications in therapy employing vitamin B_{12}.

Unlike the enzymes, which are hard to measure and which give results which must be interpreted in the light of technic used and perhaps with the particular laboratory in mind, metals can be determined with an exactness impossible in dealing with the enzymes.

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ELECTROCARDIOGRAM OF THE MONTH

The author would be pleased to receive comment and controversy from the readers in relation to explanations offered.

Inhibition of Sinus Beats by Premature Atrial Extrasystoles

This tracing was obtained from a 54 year old man with hypertension. The two strips are continuous recordings of Lead II.

The arrhythmia seems to be quite complex, but is rather easily explained. Inspection reveals that a premature contraction appears in the top tracing after three regular sinus beats. A premature P wave is visible in the T wave of the third sinus beat. However, this atrial extrasystole is blocked on its way to the ventricles. In the following long post-extrasystolic pause an A-V nodal beat "escapes." In the meantime, the normal post-extrasystolic sinus impulse is formed and the P waves appears between the QRS and the T of the nodal beat. This atrial impulse cannot be conducted to the ventricles. Following this, a normal sinus beat appears with the P wave of another atrial extrasystole superimposed on the T wave. Again the extrasystole is blocked and is followed by an A-V nodal escape beat. This identical pattern is repeated five times. Finally, at the end of the second strip, three sinus beats follow each other without an extrasystole.

This arrthythmia is possible because the first post-extrasystolic sinus beat appears with sufficient delay so that an A-V nodal escape beat can occur. The interval between two sinus beats is 0.69 second, whereas the interval between the blocked atrial extrasystole and the following normal sinus P wave is 1.04 seconds. The atrial extrasystole is conducted in retrograde direction and depolarizes the sinus node; normal impulse formation is inhibited for a considerable period of time.

Such inhibition of normal impulse formation by an extrasystole breaking into the pace maker is the more pronounced, the more the heart is damaged. Experimentally this occurs after long exposure of the heart, loss of blood, or by drugs. In clinical observation, this is seen in a variety of conditions damaging the heart.

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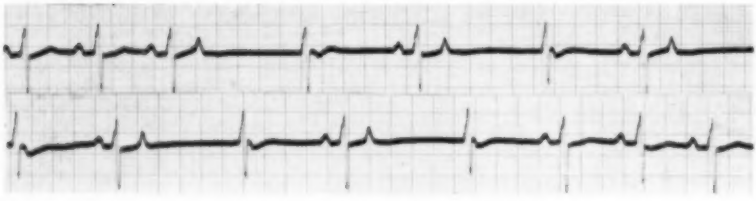
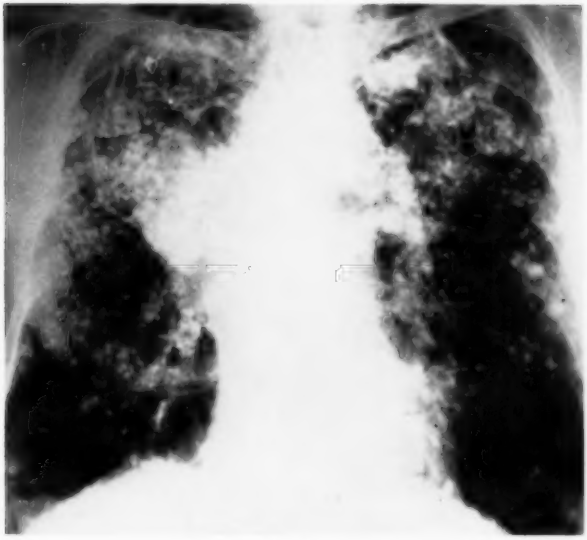


X-RAY FILM OF THE MONTH



Clinical Information

This 56 year old white man had dyspnea, increasing in severity over a period of years.

ANSWER—*Silicotuberculosis*

Multiple "egg-shell" calcifications are seen in the hilar regions. Throughout the entire chest, but more prominently in the upper two thirds, are discrete and conglomerate nodules most of which are calcified. The work history consisted of 35 years as a drill press operator in a machine shop.

Autopsy, two years later, revealed silicotuberculosis. Extensive calcifications were noted, more extensive in the upper lobes and pleura. Cavitation in the upper lobes, which appeared after these films were made, contained sequestrated calculi. Active tuberculosis was widespread throughout the liver, spleen, and lymph nodes.

Widespread parenchymal calcification, as shown in this case, is quite rare in pneumoconiosis. It is usually presumed that such calcifications are a sequel to healed superimposed infection, most often tuberculosis or histoplasmosis. On the other hand "egg-shell" calcification, in which the calcium is deposited in the periphery of lymph nodes of the hilum and mediastinum, is not rare in silicosis. In a recent review of 50 cases of silicosis at Cincinnati General Hospital they were encountered in 10 per cent. While they are, on rare occasions, encountered in non-silicotics, the combination of egg-shell calcification in the mediastinal nodes and either a positive work history or the presence of disseminated miliary lesions in the lungs is essentially pathognomonic of silicosis.

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MURRAY KORNFELD

Founder and Executive Director

American College of Chest Physicians

MURRAY KORNFELD RECEIVES 1959 COLLEGE MEDAL

Murray Kornfeld was born in New York City in 1893. He prepared for a business career and in 1912 was employed by a large export-import organization. His business career was interrupted in 1917 by tuberculosis. After several months recuperating in the Catskill Mountains, he returned to work. In 1919, he made an extended trip through South America, spending seven months in the interests of the export concern, during which time he studied economic conditions and organized branch offices there.

He continued in the export-import business until 1923 when he had a recurrence of tuberculosis. He entered a sanatorium in New York State and while there founded a magazine for patients known as "Woodland Whispers." The first issue of this monthly magazine appeared in 1924.

In 1929, after having been a patient for six years, he was invited to join the staff of the National Tuberculosis Association and spent the next two years in the publication department of that organization. During that period he travelled extensively visiting sanatoriums and talking with physicians and patients. He found that physicians were not diagnosing tuberculosis in its early stages and that many individuals were being admitted to sanatoriums for other lung conditions. These persons were classified and stigmatized as tuberculous.

To alleviate these conditions, he decided to publish a journal and to organize a society of physicians which would give the physician in the general practice of medicine the information needed to enable him to recognize tuberculosis and control more fully the treatment of this and other chest diseases. Accordingly, in 1932, he began to discuss this project with physicians wherever and whenever they would listen. After three years of pioneering, when he crossed the country from east to west and north to south, the journal, *Diseases of the Chest*, appeared in March 1935.

Soon after, it was deemed essential to form an organization of physicians to support the journal. The Federation of American Sanatoria was organized and held its first meeting in Albuquerque, New Mexico, 1935. The society was reorganized in Atlantic City in 1937 as the American College of Chest Physicians and a new set of bylaws adopted, broadening its scope. A Board of Regents was established to supervise the admission of qualified chest specialists as Fellows of the College. High standards for membership were adopted and have been rigidly maintained.

The Board of Regents of the College, meeting in New York City in 1940, adopted a resolution urging that a chest x-ray examination be given every young man inducted into the armed services. Mr. Kornfeld was authorized to meet with the Surgeons General of the Army, Navy and Public Health Service and discuss the resolution. The favorable results of this meeting were reported in the *Washington Evening Star* on June 21, 1940.

In 1942, Murray Kornfeld accepted the position as full-time Executive Secretary of the American College of Chest Physicians. Prior to that time, he had served in this capacity without compensation. At the annual meeting of the College in 1952, Dr. Otto L. Bettag proposed that his title be changed to Executive Director.

Mr. Kornfeld travelled to Havana in 1945 to establish a liaison between the College and the Union of Latin American Societies Against Tuberculosis (ULAST). This relationship has been most cordial, bringing all members of the College in the Western Hemisphere closer together. The College continues to meet regularly with ULAST and reports of College activities in the Latin American countries are presented at these meetings. He travelled through Central and South America in 1947, visiting College chapters and establishing additional chapters.

In 1949, he went to Rome to organize the First International Congress on Diseases of the Chest. This was followed by a trip to Rio de Janeiro in 1951 for the purpose of organizing the Second International Congress. In 1953, his travels took him to Spain for the organization of the Third International Congress. He went to Germany in 1955 to make arrangements for the Fourth International Congress and in 1957, he travelled to Tokyo to organize the Fifth International Congress on Chest Diseases.

During these trips, he met with the presidents and prime ministers of the various countries, as well as the ministers of foreign affairs, education and finance of the respective governments. In each country, the congress was sponsored by the government in cooperation with the chapter of the College and the medical societies.

In addition, he has organized 25 successful annual national meetings of the College, as well as numerous regional meetings.

Soon after the Silver Anniversary meeting of the College in Atlantic City this month, Mr. and Mrs. Kornfeld will leave for Vienna to organize the Sixth International Congress on Diseases of the Chest to be held there August 28 through September 1, 1960.

The degree of Honorary Fellowship in the American College of Chest Physicians was conferred upon Murray Kornfeld at the 25th Annual Meeting in Atlantic City on June 4. He has received certificates of merit from a number of countries and College chapters throughout the world.

He married Julia Hook of New York City in 1930. His son, Leonard, is with the American Embassy in Paris.

Mr. Kornfeld is a member of the Rotary Club of Chicago, the Executives Club, the Council on Foreign Relations and the Council on Pan American Affairs. He is also a charter member of the Medical Society Executives Association.

College News

DR. HAYES HONORED

Dr. Edward W. Hayes, Sr., Monrovia, California, a Past-President of the College, has been selected by the Alumni Association of Carleton College, Northfield, Minnesota, to receive the annual Alumni Achievement Award. The award was presented on June 8. Only 48 persons in the history of Carleton College have been so honored.

MINNESOTA CHAPTER

The annual meeting of the Minnesota Chapter will be held at Roberts Pine Beach Lodge on Gull Lake near Brainerd, Minnesota, July 11 and 12. Dr. Herman J. Moersch, Rochester, Minnesota, will be the featured guest and speaker. All physicians are invited to attend. Reservations may be made directly to the lodge, or to Dr. Coleman J. Connolly, 471 Lowry Medical Arts Building, St. Paul 2, Minnesota.

NEW CHAPTER OFFICERS

ALABAMA CHAPTER

President	Justus M. Barnes, Montgomery
Vice-President	James C. Nash, Decatur
Secretary-Treasurer	Kellie N. Joseph, Birmingham (re-elected)

ARIZONA CHAPTER

President	William B. Steen, Tucson
Vice-President	Lloyd K. Swasey, Phoenix
Secretary-Treasurer	Betram L. Snyder, Phoenix

CUBAN CHAPTER

President	Luis P. Romaguera, Havana (re-elected)
Vice-President	Rogelio J. Barata, Havana (re-elected)
Secretary-Treasurer	Ricardo Sanchez Acosta, Havana

FLORIDA CHAPTER

President	M. Eugene Flipse, Miami
Vice-President	Ivan C. Schmidt, West Palm Beach
Secretary-Treasurer	Charles F. Tate, Jr., Coral Gables

KANSAS CHAPTER

President	John K. Fulton, Wichita
Vice-President	Roy A. Lawson, Chanute
Secretary-Treasurer	Benjamin M. Matassarin, Wichita

MISSOURI CHAPTER

President	Ellis S. Lipsitz, St. Louis
Vice-President	Glenn O. Turner, Springfield
Secretary-Treasurer	David Nafe Kerr, St. Louis (re-elected)

OHIO CHAPTER

President	George O. Kress, Columbus
Vice-President	Giles Wolverton, Dayton
Secretary-Treasurer	Francis G. Kravec, Youngstown (re-elected)

OKLAHOMA CHAPTER

President	Philip M. McNeill, Oklahoma City
Vice-President	George L. Winn, Oklahoma City
Secretary-Treasurer	Carryl W. Wiggins, Oklahoma City

TENNESSEE CHAPTER

President	Foster Hampton, Jr., Chattanooga
Vice-President	Leland M. Johnston, Jackson
Secretary-Treasurer	Edward F. Skinner, Memphis

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President	Lawrence M. Shefts, San Antonio
1st Vice-President	Hiram M. Anderson, San Angelo
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Secretary-Treasurer	John W. Middleton, Galveston

WISCONSIN CHAPTER

President	Leon H. Hirsh, Milwaukee
Vice-President	John Rankin, Madison
Secretary-Treasurer	Raymond R. Watson, Milwaukee (re-elected)

Book Review

HOUSE OF OPEN DOORS. By Harold Holand, Director, Social Research and Publications Departments, Wisconsin Anti-Tuberculosis Association and Editor of *The Crusader*. Wisconsin Anti-Tuberculosis Association, Milwaukee, 1958. Pp. 257. Price $3.00.

It is fortunate when the history of an organization can be written by one who has been intimately associated with it for a long time and, therefore, writes from firsthand information.

Harold Holand, the author of this book, has been with the Wisconsin Anti-Tuberculosis Association nearly 30 years. He was invited to join the staff by Dr. Hoyt E. Dearholt, a pioneer and founder of the organization. He continued this close association until Dr. Dearholt died in 1939. Moreover, Mr. Holand spent three years in institutions as a patient himself which gave him an understanding of tuberculosis, which nothing else can afford.

Starting an apprenticeship with Dr. Dearholt in 1930 as a social research assistant, he manifested special interest also in editorial work. Now he is Director of the Social Research and Publications Departments and Managing Editor of *The Crusader*, the official monthly journal of the organization. There is almost no one now living in his organization who has personally known so many of Wisconsin's great leaders, who have made some of the finest accomplishments in the world leading toward eradication of tuberculosis both in people and animals.

The primary purpose of this book is to tell the story of the tuberculosis control campaign in Wisconsin over the past half century or more, particularly as it has been spearheaded by the Wisconsin Anti-Tuberculosis Association. But the book has a wider significance. The chronicle of the Wisconsin Anti-Tuberculosis Association's first 50 years might well be called a case-story of American democracy at work.

Unlike the pattern in Europe, the development of health and welfare services in the United States has not been state-inspired, but has arisen out of pioneer efforts of voluntary groups of civic-minded citizens, banding together to seek remedy of social ills. They have sponsored and carried on social research studies, fought for needed legislation, set up demonstrational projects, helped to maintain and elevate the standards of service in the official agencies they have helped to bring into being, and waged unceasing campaigns of public and (to a lesser extent) professional education.

The National Tuberculosis Association was the first of the great national voluntary health agencies and to a large extent has shown the way, organizationally and program-wise, for the other national health groups. One of its happy organizational characteristics is the fact that its state constituent associations are not considered as branch offices. These state associations have an independent existence, and much latitude in program development, although guided by the requirement of certain standards of performance in order to share in Christmas Seal revenues.

Thus, each state tuberculosis association has had much latitude in developing its own program and in experimenting in ways by which other states can profit. The Wisconson Anti-Tuberculosis Association early pioneered in campaigning for sanatoriums and public health nursing, in sending traveling clinics out on the highways, in tuberculin skin testing in schools, and in offering vocational rehabilitation services to patients in all Wisconsin sanatoriums.

In telling the Association's story, the personalities of the men and women who dreamed its dreams and fashioned with loving care the tools to bring those dreams into reality have been recreated. This necessitated much digging into old newspapers and magazines, into files of minutes of boards of directors and staff conferences, and in the reminiscences of early leaders.

Fortunately, this objective research was supplemented by the author's many years of close personal association with men and women like Dr. Hoyt E. Dearholt, Will Ross, Louise Fenton Brand, Dr. T. L. Harrington, Dr. A. A. Pleyte, and others to whom Wisconsin and the nation owe so much in tuberculosis control.

This book should be read and studied by every person who works with tuberculosis in any capacity.

J. Arthur Meyers, M.D.

ANNOUNCEMENTS

The National Institute of Cardiology, Mexico City, will celebrate the Fifteenth Anniversary of its founding on September 20-26, 1959. The Institute, in collaboration with the Mexican Society of Cardiology and the Society of Interns and Fellows of the National Institute of Cardiology, will sponsor the International Symposium on Arteriosclerosis and Coronary Disease September 20-24, and the First Mexican Congress on Cardiology, September 25-26, 1959.

The Postgraduate Division of the University of Southern California School of Medicine will present a Postgraduate Refresher Course in Honolulu and on board the SS Lurline from July 29-August 15. For further details, please write: Phil R. Manning, M.D., Associate Dean and Director, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 33, California.

A symposium on the Catecholamines in Cardiovascular Pathology will be held at the University of Vermont College of Medicine, Burlington, August 23-26, 1959. Inquiries may be directed to Wilhelm Raab, M.D., Professor of Experimental Medicine, University of Vermont College of Medicine, Burlington, Vermont.

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